WHAT PATIENT, CLINICIAN, POLICY AND SOCIO-CULTURAL FACTORS ARE ASSOCIATED WITH THE RISE IN OFF-LABEL PRESCRIBING OF DOMPERIDONE IN BRITISH COLUMBIA WHEN USED TO TREAT LOW MILK SUPPLY?

by

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the dissertation entitled:

What patient, clinician, policy and socio-cultural factors are associated with the rise of off-label prescribing of domperidone in British Columbia when used to treat low milk supply?

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ABSTRACT

This research used a case study approach to study the off-label use of domperidone when it is used to treat low breastmilk supply (LMS) in British Columbia (BC). Off-label prescribing occurs when an approved drug is prescribed for a use for which it has not been approved. Off-label prescribing is prevalent in Canada and many drugs prescribed off-label lack strong evidence of effectiveness.

My research objective was to identify the clinician, patient, socio-cultural and policy factors that are contributing to domperidone's increasing use among breastfeeding mothers in BC. Results from my research were intended to increase the overall understanding of contributors to off-label prescribing in general in order to improve its transparency, safety and effectiveness.

My four methodologies included online surveys with BC midwives and family physicians, interviews with breastfeeding mothers who had used domperidone to increase their breastmilk supply and an analysis of Health Canada's policy response to off-label prescribing. The conceptual framework for the research was a socio-ecological model incorporating patient, clinician, community/institutional, socio-cultural and policy levels of analysis.

I concluded that multiple factors at all of these levels have contributed to the rise in the off-label prescribing of domperidone to treat LMS in BC. Main drivers included clinician prescribing practices, knowledge and views of domperidone, patient needs and beliefs and the medicalization of breastfeeding.

Policy-related factors appeared to have significant influence on off-label prescribing. Health Canada does not explicitly consider potential off-label uses in drug approval documents such as product monographs nor does it systematically collect and analyse adverse drug reactions from off-label uses to identify safety concerns. Off-label uses with safety concerns are not included in post-market surveillance activities such as Health Canada safety warnings for healthcare providers and the public.

I concluded that when a drug is considered for an off-label use it should be subjected to additional scrutiny by prescribers to determine its real need and risk/benefit balance. Health Canada should systematically include off-label uses in all ADR reporting and analysis so that safety issues can be identified and responded to through post-market surveillance activities.

LAY SUMMARY

This research examined the patient, prescriber, socio-cultural and policy-related factors driving the increase in off-label prescribing of domperidone to treat low breastmilk supply (LMS) in British Columbia (BC). Off-label prescribing occurs when a drug approved by Health Canada is used for a condition for which it has not been approved. Off label prescribing is prevalent and many drugs prescribed off-label lack evidence of effectiveness.

My four methodologies included surveys with physicians and midwives, a review of Health Canada's policies overseeing drug safety and interviews with mothers who had used domperidone.

I concluded that off-label prescribing is driven by multiple factors including prescriber practices, patient beliefs and the increased medicalization of breastfeeding. A major factor is the lack of a regulatory response to off-label prescribing by Health Canada. This limitation means that the public and healthcare providers lack access to information about the risks of some off-label uses.

PREFACE

I identified the research topic and developed the design. I implemented the four methodologies, gathered and aggregated all of the data. I conducted all of the data analysis but received some statistical assistance from UBC's Statistical Consulting Services performed by Alexi Rodriguez-Arelis.

I did all the writing of the dissertation. Throughout the research I received feed-back and information from my supervisory committee members, particularly from my Primary Supervisor, Dr. Suzanne Campbell.

Some of the background information included in my research, not any results, has been published in [Currie, J. & Campbell, S. H. (2021). Domperidone to treat low milk supply: Drivers of use, efficacy, and safety. In S. H. Campbell (Ed.), *Lactation: A Foundational Strategy for Health Promotion* (pp. 193-206). Jones & Bartlett Learning]. This chapter was co-authored with Dr. Suzanne Campbell.

Ethics approval was required for this research. Approval was granted by the University of British Columbia's Clinical Research Ethics Board (Certificate No.: HI7-01786)

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GLOSSARY

ADEs – Adverse drug events

ADRs – Adverse drug reactions

CBI – Confidential business information (considered proprietary information by drug companies)

Cochrane Systematic Reviews – The Cochrane Collaboration is an international group of researchers who review and do meta-analyses on clinical trials

DIN – Drug Information Number, assigned by Health Canada once a drug has been approved

ECG – Electrocardiogram which is a test to determine the functioning of the heart

FDA – Canada – *Food and Drugs Act*

FDA – US – Food and Drug Administration

FPD – Family Practice Division (the geographical membership groups for family physicians in BC)

HRT – Hormone Replacement Therapy

LMS – Low milk supply

MAH – Market Authorization Holder – the company that applies for drug approval from Health Canada

MHPD – Marketed Health Products Directorate, a division in Health Canada

NICU – Neonatal Intensive Care Unit

NMS – Neuroleptic Malignant Syndrome

QT Interval – Interval on an electrocardiogram between the Q and T waves

RMP – Risk Management Plan

SCD – Sudden cardiac death

SEM – Socio-Ecological Model

TRU – Temporary Recommendation for Use

VA – Ventricular arrythmia

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I am very grateful for the advice, support and encouragement I received from my Primary Supervisor, Dr. Suzanne Campbell. Despite her busy schedule, she always found time to offer me practical advice, direction and the right words to keep me moving forward. I cannot thank her enough. Thank you also to my other patient and committed committee members: Dr. Joel Lexchin, Dr. Vinay Kamat and Dr. Jim Wright. It was an honour to work with all my committee members. I deeply appreciate the time you gave me and the mentoring you provided.

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I want to especially thank my friends and colleagues Dr.Sari Tudiver and Dr. Harriet Rosenburg who encouraged me to undertake a PhD and were supportive all along the way. Many thanks also to my brilliant, wonderful and inspiring children, Meran, Elise, Stefan and Linnea, who always keep me on my toes and who believed in me. A special thank-you to Elise for her advice on document tracking and editing and to Meran, a former breastfeeding counsellor, for her feedback on the mothers' interview questions.

DEDICATION

I am dedicating this work to my amazing grandchildren, Anastasia and Samuel Hoekman, who light up my life. They are already making our world a better place

And also, to:

The researchers, citizens, journalists, advocates, organizations and academics who are striving to improve the safety of prescription drugs used by Canadians.

1.0 INTRODUCTION

1.1 Focus and Purpose of the Research

This research examines the patient, prescriber, socio-cultural and policy-related factors that appear to be associated with off-label prescribing in Canada by using a case study of the off-label prescribing of domperidone to treat low breastmilk supply (LMS) among breastfeeding mothers in British Columbia (BC).

The goal of my research is to identify questions for future research and to recommend changes to Health Canada's drug regulatory policies and to clinical practices that support the safe and effective off-label use (OLU) of drugs like domperidone. This information has the potential to improve the safety and effectiveness of off-label prescribing, both in relation to domperidone and to off-label prescribing in general.

Domperidone has been approved by Health Canada to treat gastric motility problems but has been increasingly prescribed off-label in BC to increase breast milk supply (1). Lactation is an adverse effect affecting those using the drug. The growing OLU of domperidone in BC is taking place despite concerns about its effectiveness in addressing LMS and its cardiac risks as a QT-prolonging drug. Long QT syndrome is an electrical disorder of the heart that can trigger serious arrhythmias that can sometimes be fatal. Domperidone is no longer on patent and is prescribed by generic name. Generics are not promoted to physicians but may be promoted to pharmacists to ensure that a company's generic version is available.

Research indicates that 11-20% of all medications in Canada and the United States are prescribed off-label (2,3). The prevalence of off-label prescribing is much higher within some drug classes (e.g., anti-seizure medications, psychiatric drugs) and among some groups of patients such as pregnant women and children. These latter groups are often excluded from the clinical trials required for approving a drug (2). In the case of children, there may be insufficient numbers to include them in clinical trials and generate meaningful results. Most drugs prescribed off-label lack strong evidence of effectiveness (2).

There is limited Canadian research on the prevalence of and factors that drive off-label use in Canada (2). Research is lacking on clinician beliefs and prescribing behaviours related to off-label prescribing, patient understanding of and response to OLU, whether and how Health Canada policies influence off-label prescribing and the effects of broader socio-cultural influences on the practice.

The purpose of my research is to identify the factors that help drive off-label prescribing in Canada, to identify gaps in our understanding of the practice and to recommend changes to Health Canada's regulatory policies and clinical practices that can improve the safety and effectiveness of off-label prescribing in general and in relation to domperidone when it is used to treat LMS. I used a case

study approach described by Crowe et al. to explore the research questions because this approach provides the opportunity to develop an in-depth practical understanding of the prescribing and use of domperidone in its real-life context and can increase the understanding of potential policy and clinical practice gaps that may apply to off-label prescribing in general (4).

1.2 The Importance of Studying Off-label Prescribing

When a drug is tested and licensed for sale by Health Canada, it is approved to treat a specific disease or condition (the indication), using a defined dose, type of administration and targeting a specific patient group. The drug approval process requires that a pharmaceutical company follow a prescribed process for testing the efficacy and safety of a drug on the basis of clinical trials. Off-label prescribing occurs when a drug that has been approved by Health Canada is prescribed for another indication, patient group, at a dose level or method of administration that has not been approved by Health Canada. Off-label prescribing can take place because it is the provinces, not Health Canada, that regulate the practice of medicine. The provinces have delegated the monitoring and the practice of medicine to various professional Colleges such as the College of Physicians and Surgeons of British Columbia. Colleges can rule on whether a medical practice meets a usual standard of care. Ultimately, it is left to prescribers to determine whether evidence supports off-label use and to assess the benefits and risks of drugs when they are prescribed for unapproved uses.

Although pharmaceutical companies may assess the efficacy and safety of some off-label uses, the results of these studies, if they exist, may not be made public unless the company used the studies to seek regulatory approval. Even if these studies are not being used for regulatory approval, they could still be published. Fundamentally, however, there is no assurance that drugs prescribed off-label in Canada have met Health Canada's standards for drug safety and efficacy that are applied when a drug has been approved.

Off-label prescribing can be beneficial when a health condition is life-threatening and treatment options are limited. Many early treatments for HIV/AIDS involved off-label drugs because so few medications were available. However, the potential for patient harm increases when drugs are prescribed without a strong evidentiary basis. Research has also shown a higher incidence of adverse drug reactions in drugs prescribed off-label in certain situations or for certain groups when the evidence base for using these drugs is poor (5, 6).

Although physicians have the therapeutic freedom to prescribe drugs off-label, it is illegal in Canada for drug companies to directly promote off-label uses to prescribers. However, research on off-label prescribing in the United States by Kesselheim et al. (7) has established that the promotion of off-label uses to prescribers is prevalent and occurs in many forms. Drug companies in the United States have also been subject to large financial penalties for the promotion of off-label use of drugs such as anti-psychotics which caused harm to vulnerable older patients (8).

Promoting off-label drugs to clinicians can be profitable for pharmaceutical companies. Research indicates that pharmaceutical companies earn much more money from illegal promotion and sales arising from off-label prescribing than they pay in fines for this practice. In addition, conducting clinical trials for unapproved uses in order to achieve market authorization can be a lengthy and expensive process. This process can be avoided through encouraging off-label prescribing. (8).

Research indicates that the majority of drugs prescribed off-label lack strong evidence of efficacy (2, 3). A lack of scientific evidence or knowledge about a drug's safety and efficacy may lead to misprescribing and increase a patient's risk of harm (5). From a regulatory perspective, off-label prescribing undermines the standardized approval processes that Health Canada deems necessary to establish prescription drug effectiveness and safety. In essence, if Health Canada has rejected evidence for the use of specific drugs for certain indications or in certain populations, and physicians are prescribing these drugs for these indications or populations, then they are prescribing drugs in a way that Health Canada has not deemed to be sufficiently safe or effective enough to be approved in these situations.

Despite these concerns, there has been a lack of discussion and research on off-label prescribing in Canada, specifically related to the factors that drive its use. The importance of understanding the complex and interrelated drivers of off-label prescribing has been identified in a comprehensive study on the off-label use of medicinal products in the European Union (9). This study, which collected data on the prevalence of off-label prescribing and off-label policies, regulations and practices in all member states, focused on the need to understand the complex and interrelated factors that drive the rising use of off-label prescribing. This research project studied the effects of drug policies and regulations, marketplace interests, clinician and patient characteristics and needs.

This study also raised concerns, also described in an additional study by Dooms and Killock (10), that member states in Europe may believe that off-label prescribing can reduce drug costs and healthcare spending because, in some cases, drugs prescribed off-label may be cheaper than approved drugs. A common example cited is the off-label use of Avastin rather than the use of Lucentis to treat age-related macular degeneration. Another belief, not specifically supported by evidence in these reports, is that off-label uses sometimes do not bear the same research costs as approved indications and that these savings could be theoretically passed onto consumers. Weda et al. (9) have indicated that, within the European Union, there may be the possibility of reimbursement for some off-label indications.

1.3 Research Questions and Methods

I undertook a case study of the off-label use of domperidone when it is used to treat LMS in order to explore the policy, clinician, patient and socio-cultural factors that are associated with its increasing use in BC. The results from this case study were used to reflect on the limitations of

policies and clinical practices associated with off-label prescribing in general. Findings from the case study were used as a basis for recommending areas for future research and improvements to clinical practices and Health Canada's drug safety policies.

The four specific questions addressed in this research are:

1. What administrative policies does Health Canada have in place to address the safety and efficacy of off-label prescribing, in general and specifically in relation to the off-label prescribing of domperidone to address insufficient breast milk supply?
2. What, if any, policy gaps and limitations exist and how can these be addressed to improve the safety of off-label prescribing?
3. What midwife and physician practice and prescribing characteristics are associated with the prescribing of domperidone off-label to increase breast milk insufficiency?
4. What patient characteristics, needs and experiences, including socio-cultural influences, are associated with the off-label use of domperidone when it is being used to address insufficient breast milk supply?

Three methodologies were used to address these research questions. The first involved the implementation of two comparable online surveys, one with BC family physicians and the other with BC licensed and practicing midwives, who treat LMS. The surveys, which were managed and implemented separately, gathered information on clinician demographic and practice characteristics, methods used to treat LMS, including the use of domperidone, and clinician views of the drug's evidence, safety and effectiveness. Licensed midwives in BC received the authority to prescribe a selected group of drugs**,** including domperidone**,** in 2009 (11).

The second methodology involved the implementation of qualitative, semi-structured interviews with breastfeeding mothers who had used or were still using domperidone to address LMS. These interviews gathered information about mothers' experiences with breastfeeding, LMS, domperidone use and outcomes and the factors that contributed to its use. Socio-cultural factors and institutional and community factors that contributed to the use of domperidone were also explored in these interviews.

The third methodology involved a review of Health Canada's administrative policy and regulatory documents to identify its policy responses to off-label use and to the use of domperidone related to its OLU as a treatment for LMS. The policy review was supplemented with interviews with staff from Health Canada's Marketed Health Products Directorate (MHPD), interviews with two Canadian health and legal policy experts and an academic and grey literature review.

1.4 Organization and Structure of this Document

Chapter 2.0 provides a description of the conceptual framework I used as the frame of reference for my research and the results of the literature review. Chapter 3.0 presents the results of

the online surveys conducted with BC family physicians and practising, licensed midwives. This chapter provides an overview of the planning, recruitment and selection processes for the surveys with findings being reported from each survey separately.

Chapter 4.0 reports the results of the open-ended, semi-structured qualitative interviews with breastfeeding mothers who used domperidone to treat LMS. The chapter includes the personal, medical, familial and socio-cultural factors that mothers associated with their experiences with LMS and with their domperidone use.

Chapter 5.0 describes the results of a review of Health Canada's administrative policy documents and the academic and grey literature and interviews with key experts and Health Canada officials which explored the regulatory and policy context of off-label prescribing and the OLU use of domperidone to treat LMS.

Chapter 6.0 presents the key conclusions arising from the research including a discussion of the key interrelationships between the findings emerging from the three methodologies. The triangulation of the methods and of the data arising from each method, provide a comprehensive overview of the factors that have influenced the off-label prescribing of domperidone to treat LMS and identifies areas where the results converge or diverge. This chapter also identifies key areas for future research and recommendations for improvements in Health Canada's policy responses to off-label prescribing and in healthcare practices related to the treatment of LMS.

2.0 RESEARCH BACKGROUND AND LITERATURE REVIEW

2.1 Introduction and Description of the Conceptual Model

Chapter 2.0 includes two sub-sections. Section 2.1 includes a discussion of the different conceptual models I considered for my research and the characteristics and appropriateness of the Socio-Ecological Model I selected. Section 2.2 summarizes the results of a literature review that relate to the key questions I explored in my research. This includes a discussion of the characteristics, prevalence, safety, and monitoring of OLU, the characteristics of LMS including the factors contributing to its diagnosis and information on the safety and effectiveness of domperidone in general and when it is prescribed off-label to treat LMS.

Several health behavioural models were reviewed in order to select an appropriate and relevant conceptual framework for my research. These included the Socio-Ecological Model (SEM), the Transtheoretical Model, the Health Belief Model and the Theory of Planned Behaviour (TPB) (12, 13). The characteristics and appropriateness of these models were discussed with my primary research supervisor.

The Transtheoretical Model is based on an individual's response to interventions and relates to the theory of pre-determined stages of change. The Health Belief Model is based on how the readiness of individuals to respond to health issues is shaped by an individual's beliefs, including their assessment of risks, benefits, barriers and a sense of self-efficacy. The TPB examines how beliefs and attitudes shape individual intentions and behaviours, within the context of social norms. It is again based on individual characteristics and is linked to self-efficacy. This model has been used to examine specific breastfeeding behaviours, for example, whether and how an individual's sense of self-efficacy influences breastfeeding duration.

The Transtheoretical, Health Belief and TPB models focus primarily on the characteristics, intent and motivations of individuals and how these shape responses to a specific health intervention. My focus was not primarily on the individual but on how individual behaviour interacts with multiple environment factors such as institutional, clinical practices, health policy and socio-cultural influences such as medicalization. I was interested in seeing how these factors contributed individually and in relation to each other to influence the OLU use of domperidone to treat LMS. The Socio-Ecological Model more clearly reflects this interdisciplinary and multi-factorial focus.

McLaren et al. (14) describe the social ecological model as 'a framework or set of theoretical principals for understanding the dynamic interrelations among various personal and environmental factors in health.' According to the authors, this perspective, '…emphasizes the multiple dimensions (for example, physical environment, social and cultural environment, personal attributes), multiple levels (for example, individuals, groups, organizations), and complexity of human situations (for

example, objective and subjective qualities, various scales of immediacy, cumulative impact of events over time)' (p.12).

A premise of ecological models is that changes in behaviours are influenced by factors within all of these levels. Conceptual models are also considered to be useful guides for identifying effective change interventions after an analysis is complete. Using a Socio-Ecological Model reflects the interdisciplinary nature of my research which is based on the premise that factors at multiple levels, (prescriber, patient, socio-cultural and public policy), contribute independently or in combination to the off-label prescribing of domperidone to treat LMS.

Ecological perspectives reflect the complexity and interrelationships that exist in the natural ecosystem. Ecological models (including socio-ecological models) have been used in diverse fields to gain a more comprehensive understanding of the multiple personal and contextual factors that contribute to understanding a behaviour.

The use of ecological models in the health field arose from an acknowledgement of the complexity of public health issues and the need to understand physical, social, cultural and historical aspects of context in addition to the characteristics and behaviours of individuals. SEMS were seen as a model that is potentially less narrow and linear than traditional models establishing causality found in traditional epidemiological research. According to Sallis and Owen, 'The typical goal of experimental designs – to isolate a single intervention from the effects of its context – is conceptually at odds with the ecological emphasis on studying how intervention components interact with their context' (15: p.59).

Socio-ecological models are frequently used to describe the multiple determinants contributing to common and high-risk health behaviours in order to identify comprehensive and effective interventions. SEMS have been used to analyze the personal and environmental factors contributing to tobacco use, obesity and to sedentary lifestyles that contribute to health problems.

In addition to understanding the personal and contextual factors that influence behaviour, a strength of a SEM is its potential to identify the 'key leverage points and intermediaries for health promotion within organizations' (16: p.1). Multi-level interventions involving both personal and environmental factors may be more successful and sustainable than single-level interventions based primarily on individual change. It is for these reasons that I selected the SEM as the most appropriate conceptual model for my research. This decision was approved by my research committee.

A major limitation of ecological models is that they are not always able to identify the factors that are most influential in affecting behaviour within or between multiple levels or to specify the primary interactions between variables that occur. This may affect the ability of a SEM to help define future research needs or identify and implement evidence-based health interventions. As noted by Sallis and Owen, these models 'broaden perspectives without identifying specific constructs or

providing guidance about how to use ecological models to improve research or interventions' (15: p.58).

Hertz (17) notes that bridging different disciplines or theories into one social-ecological framework can be challenging. This is due to the differences in theory orientation, perspectives and language within different disciplines. The development of an ecological model involves cross disciplinary knowledge so that no single theory is likely to drive an ecological model with diverse, multi-level components. These limitations can also affect the selection of effective interventions or the clear identification of testable hypotheses arising from using these models.

2.2 The Development of the Socio-Ecological Model

To develop a SEM most appropriate to my research questions, I completed a focused review of the literature on socio-ecological models and reviewed four different SEM frameworks (16,18 – 20) that were used to research health-related behaviours that broadly related to my research questions. Each of these models used somewhat different levels and components for analysis. I then considered the applicability of these models and levels to my primary and secondary research questions in order to help determine the levels of analysis (see Table 1).

Table 1: Elements Found in Four Socio-Ecological Models (SEMs)

References	Study Purpose	Number of Levels of Analysis	Description of Levels of Analysis
Baral et al. (18)	Assessment of the risks and risk contexts of HIV epidemics	5	1. Individual – biological factors associated with the acquisition of HIV 2. Social and sexual networks 3. Community – prevention, treatment and care services 4. Public policy – content and implementation of policies promoting or reducing risk 5. HIV epidemic state
Dunn et al. (19)	Assessment of the barriers and positive contributors to breastfeeding	5	1. Individual – expectations, knowledge, history 2. Interpersonal – influence of social relationships 3. Community – social norms 4. Organizational – support from healthcare providers 5. Policy – legal and policy
Tannenbaum et al. (20)	Reducing potentially inappropriate medication in older Canadians	3	1. Patient, caregivers, public 2. Health care providers 3. Health-related organizations
UNICEF – Communication for development (16)	Identification of personal and institutional leverage points for health promotion initiatives within organizations	5	1. Individual – knowledge, attitudes and behaviours 2. Interpersonal – families, friends, social networks 3. Community – relationships between organizations 4. Organizational – organizations and social institutions 5. Policy and enabling environment – including laws

I incorporated the five core premises in the planning of my model identified by Sallis and Owen (15) as being essential to developing and interpreting a SEM. These are that:

1. Multiple levels related to personal and environmental/contextual factors all play a part in influencing health behaviours and need to be included in the model. I developed a conceptual model with six levels to take into account the multiple factors that could drive the increasing use of domperidone to treat LMS.
2. Environmental factors such as those related to the community or the policy and enabling environment are significant determinants of health behaviours and may be more important than individual characteristics because they shape personal responses.

3. Variables within and outside of different levels of the model interact and influence each other. Understanding these interactions is an important aspect of data analysis. A major caveat is that while socio-ecological models can identify factors and potential associations, these factors and associations cannot be verified until they are examined in more detail.
4. Ecological models need to be behaviour-specific in order to guide research and recommend relevant interventions. Clinician characteristics and prescribing behaviours, the influence of patient needs, beliefs, knowledge and expectations, institutional and socio-cultural influences and the effects of public policy as the enabling context are the behavioural and subject specific items represented by levels in the SEM.
5. A SEM is the most appropriate way to develop recommendations that address practices and policies because of its interdisciplinary approach. Recommendations included in my research address future research priorities and changes in the areas of policies and clinical practices related to off-label prescribing and the use of domperidone to treat LMS.

Table 2 describes the six levels of the SEM that I developed as the conceptual framework for my research. My methodologies addressed the elements of each of these levels. In my analysis of findings, I combined the results emerging from the community and institutional levels. These levels and their elements were discussed with and approved by my research committee.

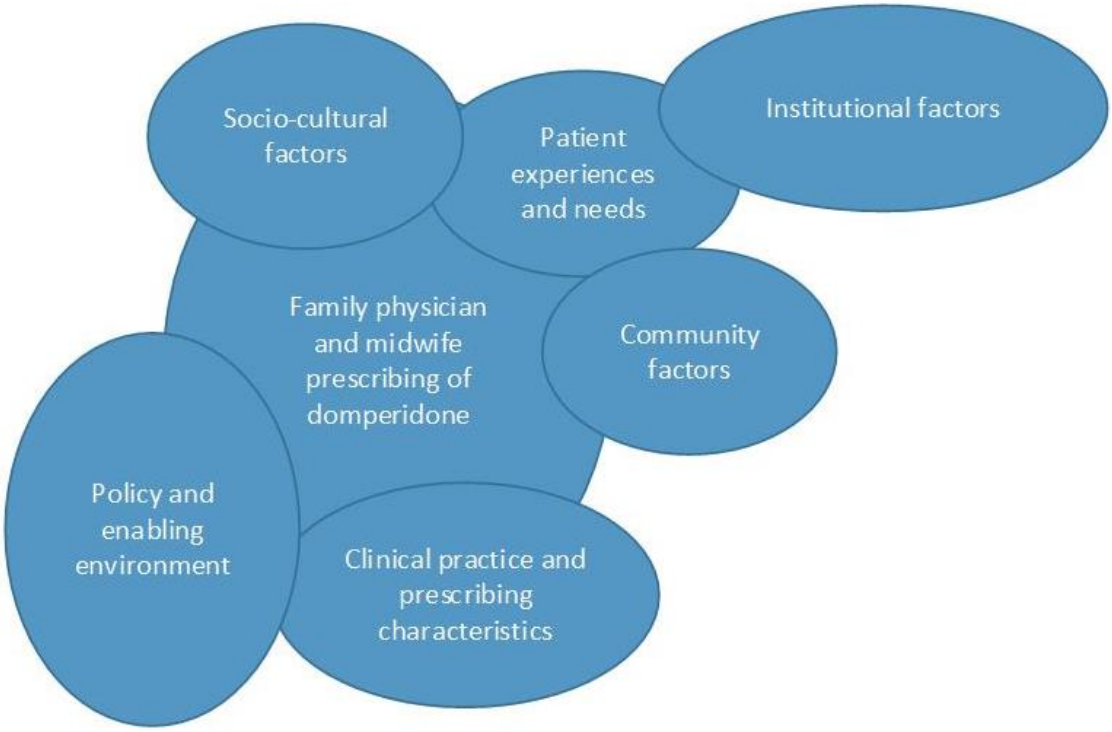
Table 2: Levels of Analysis Included in the SEM

Level	Level Description	Topics Included	Methods
1	Clinician/prescriber level: BC family physicians and licensed, practicing midwives	Prescriber knowledge, attitudes, beliefs, clinical practice and prescribing characteristics, views of domperidone's safety, level of use, approaches to diagnosing and treating LMS, response to Health Canada Advisories and OLU.	– Two online surveys: BC midwives and family physicians
2	Patient level: Breastfeeding mothers who have used domperidone	Patient characteristics, breastfeeding beliefs and expectations, impacts and diagnosis of LMS, use and impacts of domperidone, relationship with healthcare providers, awareness of OLU	– Qualitative open-ended semi-structured interviews with mothers who have used domperidone
3	Community level	Role of community-based healthcare providers in diagnosing LMS and providing help and educational resources. Role of lactation consultants	– Interviews with breastfeeding mothers who have used domperidone – Literature review

Level	Level Description	Topics Included	Methods
4	Institutional level	Hospital policies including early infant contact, breastfeeding support, interpretation of infant weight loss, early interventions, healthcare provider support and impact of early discharge	– Qualitative interviews with breastfeeding mothers who have used domperidone – Literature review
5	Socio-cultural factors	Socio-cultural factors affecting mothers' expectations of breastfeeding, information environment and medicalization of breastfeeding	– Qualitative interviews with breastfeeding mothers who have used domperidone – Literature review
6	Policy and enabling environment	Health Canada regulations and administrative policies that are relevant to off-label prescribing and use	– Policy analysis – Key respondent interviews – Online surveys of midwives and family physicians – Interviews with key experts and Health Canada officials

Figure 1 is a conceptual presentation of the levels in the SEM and their potential interrelationships. This figure is included as a visual representation of the levels I explored through my methods and analysis. It does not reflect the comparative weight or influence of the different levels or all the interrelationships between them. Family physicians and midwives are placed in the central bubble because they are the agents of prescribing all prescription medications, including domperidone.

Figure 1: Conceptualization of the Socio-Ecological Model (Janet Currie 2020)



2.3 Off-label Prescribing

2.3.1 Description

When a drug is approved and licensed for sale by Health Canada it is specified for a specific indication, dose level, method of administration or patient group. An indication is a specific disease or condition that the drug is licensed to treat. Many drugs are approved for multiple conditions and additional indications can be approved at a later date through the regulatory process.

A drug can only be authorized if a drug manufacturer files an application with Health Canada and after the company has undertaken a series of tests and clinical trials to assess the drug's potential toxicity, appropriate use, efficacy and safety and whether it was made using good manufacturing practices.

Every prescription and over-the-counter (OTC) drug approved and marketed in Canada must carry a specific Health Canada approved product label. This is a written report for a specific approved product that provides detailed information about the drug including its directions and indications for use, dosage information, route of administration, results of clinical trials and warnings and cautions. The product label is focused on approved indications and cannot include promotional material. Components of the drug label are included in specific documents related to the drug. One of the most important documents arising from the drug approval process is the Product Monograph. This

document, which is prepared by the drug manufacturer and approved by Health Canada as part of the drug approval process, provides information about the licensed drug's actions, purpose, contraindications, potential side effects and proper use.

Off-label prescribing occurs when a drug that has been approved and licensed for a specific condition (indication), dose level, method of administration or patient group is prescribed for another purpose, at another dose level, method of administration or patient group for which that drug has not been approved. Off-label prescribing is common; 11 – 20% of all drugs prescribed in the US and Canada are prescribed off-label. There is a higher prevalence of off-label prescribing among certain drug classes or for certain conditions. (2,3). In some cases, drugs prescribed off-label are the predominant treatment for certain conditions. Wittich et al. (21) provides examples of off-label prescribing practices that have become standards of care, including the use of aspirin as an antithrombotic agent.

Off-label prescribing by healthcare providers is not prohibited. Under the Canadian constitution, it is the provinces, not the federal government, that regulate the practice of medicine. Provincially legislated professional bodies, such as the College of Physicians and Surgeons of British Columbia, are assigned this regulatory responsibility. These regulatory authorities leave it up to prescribers to assess whether the clinical evidence associated with a drug prescribed off-label supports its use. As stated by Dooms and Killock, 'Off-label prescribing is therefore strongly associated with the principal of therapeutic freedom according to which a physician may make an assessment of the suitability of a medication based on his or her understanding of a particular patient's medial condition, history and social circumstances' (10: p.18).

The authors note that, in some jurisdictions, case law has recommended constraints on the therapeutic freedom that underpins off-label prescribing. European case law, (*Commission vs Poland*), has recommended that drugs should only be prescribed off-label when no authorized drug is available to treat the condition, that there must be sufficient evidence to prove the drug's effectiveness and safety and that, prior to prescribing, the prescriber should undertake a process of informed consent with patients.

Although the prescribing of off-label drugs is legal, drug regulators such as Health Canada prohibit the promotion of off-label uses to physicians or the public. The concern is that marketing could encourage the widespread use of drugs in settings where their efficacy and safety have not been rigorously tested, exposing patients to uncertain benefits and possible adverse effects.

Off-label prescribing is complex and involves multiple drivers. As is noted in the most comprehensive report on off-label prescribing as it occurs within the member states of the European Union,

> ‘ . . . in many cases, it is not a single driver, but rather a combination of drivers that provoke off-label use. Drivers may also change during the life cycle of a medicinal product that is used off-label. Overall, the nature of the drivers is sometimes complex and drivers may interact with each other, however the relative contribution of, and interaction between, the different factors is unknown’ (9: p.10).

This report provides an overview of the main drivers of off-label prescribing in the European context. These include drivers at the patient, healthcare provider, health care system and the regulatory levels. At the regulatory/policy level, the study identifies the drivers of off-label prescribing to include limited incentives for manufacturers to extend the label or to undertake a drug authorization process, the narrowing of indications, and the lack of adequate information for the public on non-approved or withdrawn indications.

At the post-market drug authorization stage, drivers can include prescribing off-label drugs to address drug shortages or unavailability and the lack of incentives or requirements for drug manufacturers or regulators to monitor off-label drug efficacy. This study suggests that a growing reason for off-label prescribing in the European Community may be because some off-label uses of drugs may be cheaper than approved drugs for the same condition or because off-label uses may be illegally promoted by drug companies. Pharmaceutical companies may seek to broaden their potential for profit by indirectly promoting off-label uses, especially if the approved uses of a drug are narrow.

Patient and professional characteristics, needs and expectations also play a significant role in off-label prescribing. Healthcare providers may prescribe drugs off-label when treatment options are limited, in cases where clinical guidelines recommend off-label drug use or when an off-label drug continues the treatment initiated by an approved drug. Weda et al. (9) also suggest that off-label prescribing may reflect poor prescribing practices that are not based on evidence.

According to Chen et al. (22) many physicians may be unaware that a drug they are prescribing is off-label. In a national US study, the authors found that 40 – 50% of physicians had trouble identifying whether a list of commonly used medications were being prescribed for approved or unapproved indications. The authors concluded that if a physician believes a drug has been approved when it has not, they may overestimate the degree to which the drug is safe or effective.

> Weda et al. (9) also noted that patients may influence their healthcare provider to prescribe a drug off-label. This may be because the patient has a serious health condition for which no effective treatment appears to exist, or if it does, has unacceptable adverse effects. An off-label drug may be cheaper or a physician may also consider it to be more effective than existing treatments.

Off-label prescribing can occur when there is limited treatment for conditions experienced by specific population sub-groups. For example, off-label prescribing may be more common in cases of rare or orphan diseases where the number of patients is relatively small and treatment options are

limited. As noted by a report on off-label prescribing completed by the Canadian Senate's Standing Committee on Social Affairs, Science and Technology**:**

> 'Of particular concern is the fact that children, the elderly and pregnant and nursing women are seldom included in clinical trials sometimes due to ethical considerations or to multiple medical conditions. As a result, many of the approved drugs that they are prescribed are done so without the benefit of any safety and effectiveness data for their population sub-group. Thus, out of necessity, off-label drug use is common among these sub-groups of the population as there may be no alternative' (23: p.10).

Quebec research looking at off-label prescribing to adults and US research that looked at off-label prescribing to both adults and children concluded that 11 – 20% of all medications are prescribed off-label (2,3). The prevalence of off-label prescribing can be much higher when specific drug classes and patient groups are considered. Eguale et al. (2) found that the three drug classes where off-label prescribing was most common were drugs involving the central nervous system (26%), anti-infectives (17%) and medications for ear/nose and throat conditions (15%).

Studies of off-label drug prescribing in specific settings or with specific patient groups also confirm high rates of off-label prescribing. A study of the frequency of drugs prescribed off-label in the antenatal unit of a large urban hospital in Liverpool found that 74% of the prescriptions for mothers were off-label and 13% of these involved drugs that posed high risks (6).

The prescribing of off-label medications to children is common. A study of the frequency of off-label prescribing to children from 0 – 17 years in US outpatient settings, found that 62% of outpatient visits included drugs prescribed off-label (24). In a study using data from US-managed care plans, Czaja and Valuck (25) found that 70% of the antidepressants prescribed to children and adolescents were considered to be off-label when approved indications were matched with diagnoses.

In an analysis of European studies on off-label prescribing involving adults and children in EU member states, Weda et al. (9) found that off-label prescribing rates for children in in-patient settings ranged from 13 – 69% (32 studies) and from 2 – 100% in outpatient settings (40 studies). In the adult population, the prevalence of off-label prescribing ranged from 7 – 95% (23 studies) in inpatient settings and 6 – 72% for outpatients (13 studies).

Research suggests that many off-label uses lack strong evidence of effectiveness. In a study of the prescribing records of a network of Quebec-based family physicians, Eguale et al. (2) found that 79% of the off-label prescriptions written by a Quebec network of family physicians lacked strong evidence. Among drugs prescribed for central nervous system conditions, 82% were described as having no strong evidence of effectiveness. Eguale's data is comparable the analysis by Radley et al. of off-label prescribing among US office-based physicians where the findings indicated that 61 – 84% of the off-label prescriptions had little or no scientific support (3).

Although off-label prescribing can be beneficial, especially when no other treatment options exist, without systematic testing for efficacy and safety, the use of off-label drugs may expose patients

to a type of uncontrolled experiment with the potential for causing harm (26). Some research indicates that off-label prescribing may also lead to a higher proportion of medication errors, leading to additional harm in some patients (27).

A study of the prevalence of adverse effects associated with off-label use in an adult Intensive Care Unit (ICU) population found that 43% of the drugs prescribed were off-label. Smithburger et al. (28) concluded that adverse drug events (ADEs) and the severity of these events do not occur more frequently with off-label than with on-label use but that the risk of ADEs increases by 8% for every off-label medication used. Although the level of evidence for the off-label uses examined in this study was not a central focus, almost 60% of the medications involved with the top 25 off-label indications were identified as a possible therapeutic option in at least one treatment guideline.

Eguale et al. (5), in a study of five years of prescription records in primary care clinics in Quebec, found a rate of off-label prescribing of 11.8% with 81% of off-label prescriptions lacking strong evidence. When drugs were prescribed off-label and lacked strong scientific evidence, the rate of adverse drug events (ADEs) was higher than when drugs were prescribed on-label. The authors concluded that, ' . . . the lack of approval from a regulatory body implies a lack of safe dosage ranges and inadequate information on contraindications, which in aggregate, make ADEs more likely' (p.60).

Off-label uses that are illegally promoted by drug companies can have harmful effects for large groups of people. Hormone replacement therapy (HRT), which consisted of various combinations of estrogen-progestin, was increasingly prescribed and unethically promoted to menopausal women to prevent conditions as diverse as dementia, heart disease and breast cancer as well as to treat menopausal symptoms. The deliberate indirect promotion of these off-label uses through mechanisms such as ghostwritten articles in medical journals led millions of women to use these drugs, believing their risks to be minimal and their benefits to be significant. In 2002, a large-scale US national randomized trial concluded that, in fact, HRT did not prevent but instead contributed to heart disease, stroke and breast cancer (29).

Some research suggests that off-label prescribing may lead to more medication errors. Rinke et al. (27) in a study of pediatric antidepressant medical errors from reports in a national reporting database, found that 77% of the error reports involved off-label medications. The majority of these errors were related to administering or dispensing. Ninety-five percent (95%) of all errors reached the patient and 6.4% required increased patient monitoring or additional treatment (p.27).

The identification of patient level harms arising from off-label prescribing is often limited because current pharmacosurveillance methods do not provide timely information on the health condition of the patient and whether the condition that the drug is used to treat is being prescribed on or off-label. Eguale at al. (30) discuss how electronic prescribing systems could be improved to systematically track off-label uses and inappropriate prescribing. Up to now, most administrative

databases lack this capacity, because it requires that healthcare providers be able to identify whether any drug that they are prescribing is for an off-label use or for an approved indication.

Although the promotion of off-label prescribing in Canada is not legal, evidence from the United States indicates that off-label uses are promoted to physicians routinely. Kesselheim et al. (7), in a review of whistleblower complaints about off-label promotion by pharmaceutical companies in the United States, identified four types of illegal promotion involving physicians that were common. Most of these promotional efforts involved extending the drug's use to unapproved diseases and conditions.

According to the author, a common method of promoting off-label use included pharmaceutical representatives extolling the value of a drug for an off-label use to physicians in meetings, educational sessions and journals. Other strategies included identifying patients through physician records who already use or could use drugs prescribed off-label in order to target sales. Providing free samples of drugs used off-label to physicians and promoting online information for patients on off-label uses were other common off-label prescribing promotional strategies.

Mello et al. (31) identified examples of informal methods of promoting off-label prescribing for specific drugs. These included using key opinion leaders (KOLs) to promote the potential of off-label uses to physicians. Fugh-Berman and Melnick (26) describe the use of meeting abstracts or posters, often published in conference proceedings or non-peer reviewed industry sponsored supplements, as other common approaches.

The widespread and illegal promotion of off-label uses has had implications for patient safety and the costs of delivering healthcare. A report that examined 25 years of criminal and civil penalties, totaling $US 35.7 billion, brought by US state and federal governments against pharmaceutical companies, found that 25% of the penalties involved the illegal promotion of drugs for off-label uses (8). One of the largest penalties (US$2.2 billion) for off-label promotion was levied against Johnson & Johnson for its promotion of the anti-psychotic risperidone which is approved to treat schizophrenia and psychoses. The company provided inducements to Omnicare, a large national pharmacy in the United States that provides services to nursing homes to switch patients to risperidone as a means of managing the behaviours of patients with dementia, an off-label use. Risperidone increases the risk of stroke and diabetes, adverse effects that were well known to the manufacturer. In many cases, the costs of treating these long-term health conditions fell upon state governments (32).

In Canada, Diane-35, a drug approved by Health Canada for severe acne, was actively promoted by the manufacturer to Canadian women for its contraceptive properties, an off-label use. It became increasingly prescribed to young Canadian women for this reason despite its potential for causing blood clots (33) more frequently than other oral contraceptives. At least 13 Canadian women died from blood clots attributed to this off-label use (34).

2.3.2 Regulatory Responses to Off-label Prescribing

Off-label prescribing does not appear to be specifically regulated by Health Canada. There is no clear process for identifying and tracking off-label uses, no requirement to test for the effectiveness and safety of off-label use once these have been identified, and no systematic way of collecting information on the adverse effects of drugs prescribed off-label. Risk communication messages issued by Health Canada do not routinely address concerns or make recommendations about off-label uses. New legislation and regulations passed under *Bill C-17* under Canada's *Food and Drugs Act* (35) include provisions whereby the Minister of Health can order safety studies or withdraw a drug if the public's health is considered to be at risk. However, the applicability of these laws and regulations to off-label prescribing is unclear. Health Canada's policy responses to off-label prescribing are discussed in more detail in Chapter 5.0.

In the United States, the Food and Drug Administration (FDA) appears to be moving towards a more minimal role in regulating the illegal promotion of off-label prescribing. This has been a response to several court challenges, brought by industry-friendly groups. These cases concluded that that FDA guidance documents on off-label prescribing violated commercial free speech protections (36) and the FDA declined to appeal the decisions to a higher court.

In Canada, although drugs can be tested by drug manufacturers for some off-label indications, there is no assurance a drug used off-label has gone through the complete clinical trial testing process unless a drug company seeks approval for the drug. In some cases, drug manufacturers test for off-label indications, but later abandon filing for drug approval or they may seek approval which is then rejected. In these latter cases, the clinical study reports are now made public.

In addition, if a drug is off-patent and being sold in generic form there may be no financial incentive for a drug company to test for off-label uses. This is because, after a patent has expired, multiple companies are able to sell a generic version of a drug. A company undertaking the clinical trials in order to gain approval for an off-label indication may not reap benefits in terms of increased sales. Even when a drug has been tested for off-label uses, the public does not have access to information on whether it could have met the requirements for regulatory approval unless the manufacturer seeks approval for these indications. Stafford describes a comparable situation in the US:

> 'Though new indications may be added to a drug's label through a supplemental new drug application, this occurs infrequently; generic drugs lack a corporate sponsor to bear the required expenses, and for brand-name drugs that are already widely used off-label, conducting costly clinical trials that could produce non-supportive evidence is a potentially risky business decision' (37: p.1).

Rodwin (38) sees the current regulatory environment for off-label prescribing as undermining the mission of drug regulators like the FDA which is to, ' . . . protect patients from dangerous and

ineffective drug therapies. It also compromises the medical ideal that physicians should prescribe medications based on the careful evaluation of the risks and benefits' (p.5).

According to some researchers, off-label prescribing also gives pharmaceutical companies the opportunity to 'game' the system, by seeking authorization for secondary indications that involve less complicated and less expensive clinical trials with the intention of later promoting off-label uses once the drug is approved. As noted by Fugh-Berman (26):

> 'If extensive off-label use is anticipated, a company may seek approval for a narrow indication in order to speed a drug to market. In other words, a drug may be approved for a decoy indication while an extensive off-label campaign is not disclosed to regulators. For example, a company that plans to promote a drug off-label for cancer prevention could avoid the costs and delay that a long-term trial entails by instead funding a relatively inexpensive trial of ulcer treatment, or, even better for business – rabies. Rabies is rare, and in the US, treatments for rare diseases are *orphan drugs,* eligible for expedited six-month reviews. Orphan drugs enter the market faster' (p.433).

Off-label prescribing also puts more onus on physicians to be able to differentiate between on-label (approved) and off-label uses of drugs and to assess their potential for harm in the absence of systematically collected safety data (39).

2.3.3 Approaches for Improving Off-label Prescribing

Weda et al. (9) undertook a study looking at the implementation, safety and efficacy of off-label prescribing in the 27 member states of the European Union. The report discussed a range of regulatory, healthcare system and professional/patient approaches for improving the practice. Health Action International (HAI), a European-based non-profit organization that conducts research and advocacy supporting the safe, effective, affordable and accessible use of medications, summarized and prioritized the approaches for improving off-label prescribing that emerged from this report and related research (40).

HAI concluded that, although off-label prescribing is sometimes justified, the practice undermines the drug authorization system and raises questions about the level of evidence for off-label uses and patient safety because most of these uses have not undergone the benefit/harm assessments that occur with approved drugs. HAI's recommendations for the improvement of off-label prescribing address off-label monitoring, education, patient consent, compensation and public funding approaches. Table 3 summarizes key recommendations from this report.

Table 3: Proposals for Improving Off-label Prescribing in Europe

Level of Policy	Description
Regulatory	▪ Regulations to reflect the exceptionality of off-label prescribing. ▪ Off-label prescribing to be driven by patient needs and informed consent. ▪ Improved data gathering and monitoring of off-label prescribing including the more frequent use of patient registries for vulnerable patients. ▪ Increased government monitoring and sanctioning of the illegal promotion of off-label prescribing.
Healthcare system	▪ Development of user-friendly OLU reporting options to improve reporting levels. ▪ Compensation for victims of serious ADRS (adverse drug reactions) arising from off-label uses. ▪ More public funding of clinical trials that can identify off-label uses of drugs. ▪ Adoption of measures to support/incentivize manufacturers to register off-label uses where data has been submitted and where there is a favourable benefit to harm ratio.
Professional/patient	▪ Development of information campaigns on off-label prescribing for patients and professionals. These would include raising the awareness among healthcare providers about the illegal promotion of off-label uses and the promotion of off-label prescribing by industry to medical students.

France is one jurisdiction that has tried to develop a specific regulatory response to off-label prescribing that reflects some of the recommendations found in the HAI report. The development of Temporary Recommendations for Use (TRU) grew out of serious health problems that arose from the off-label prescribing of benfluorex (Mediator). This drug, which was on the market for 30 years in France, was frequently prescribed off-label for weight loss. It led to cardiac valve damage resulting in approximately 1800 deaths and 4200 hospital admissions (41).

A TRU provides a temporary authorization for off-label drug uses for three years in order to give drug manufacturers sufficient time to expand its marketing authorization. During this time, the manufacturer is expected to actively collect data on the drug's adverse drug effects, submit them to the drug authority in three months and undertake and fund a patient monitoring program. A TRU is renewable and has a strong economic incentive for pharmaceutical companies because if one is granted, it enables manufacturers to be reimbursed for the drug through national insurance(42).

Research indicates that, although TRUs have been available since 2012, only six had been issued by 2015 (43). The first TRU, issued by the French drug agency, was for baclofen a drug approved to treat spasticity, a motor/muscle disorder, but is commonly prescribed off-label for alcohol

dependence, often at high doses and with concerns about its effectiveness (44,45). When the implementation of the TRU for baclofen was analyzed, it was found that only a small proportion of patients were registered for follow-up and the monitoring of prescriptions by physicians was poor (45). Naudet et al. (44) suggest that, although the TRU required increased ADE (adverse drug event) monitoring of baclofen's safety, recent evidence has shown an increased rate of hospitalization and death from the use of the drug (p 410).

Braillon and Lexchin (45) suggest that the lack of effectiveness of this TRU resulted from France's national drug agency being unwilling to address serious breaches in its implementation. The authors also note that the poor registration of patients receiving the drug indicates that prescribers are ' . . . not troubled by off-label drug use despite the sometimes-serious consequences' (p.890). They state that:

> 'Merely setting up a program that gives companies time to produce evidence to justify off-label uses of drugs is not an adequate response to the problem of off-label prescribing. Regulatory agencies and clinicians need to take responsibility for effectively dealing with this issue. Off-label use is very occasionally a useful liberty; it must not continue to be anarchy' (p.891).

2.3.4 Physician and Public Awareness of Off-label Prescribing

The degree to which physicians or other prescribers are knowledgeable about off-label prescribing has been relatively unexplored in the literature. Research suggests that while physicians are familiar with the concept, they may underestimate the degree to which off-label prescribing is common. As was previously noted, Chen et al. (22) found that only 40 – 50% of the physicians in their study were able to identify whether the prescribing of drugs for specific indications was off-label.

In a systematic review, Balan et al (46) looked at the awareness, knowledge and views among physicians, pharmacists, pediatric nurses, parents and children of off-label prescribing. Eleven studies were included in the review. The six studies focused on physician prescribing found that while most doctors, (69 – 93%), were familiar with the concept and the term 'off-label prescribing', most were unaware that off-label prescribing was common in general practice.

In a specific study of the attitudes and experiences of 202 general practitioners who prescribed drugs off-label to children in Scotland, Ekins-Daukes et al. (47) found that 74% of the respondents said they were reasonably familiar with the concept of off-label prescribing although 53% were unaware the practice is commonplace. More importantly, only 40% of the physicians said that they knowingly prescribed drugs off-label, even though many of their patients were children for whom many drugs are prescribed for off-label indications.

The sources that physicians in this study used to find information about off-label uses were not strongly evidence-based. Most of the physicians used The British National Formulary for information about off-label uses although the study noted that the information in this pharmaceutical reference text

was often not up-to-date. Eighty percent (80%) of the physicians relied on their own previous clinical experience to determine whether a drug use was off-label. Although 50% of the physicians in the study wanted more information on pediatric dose levels, only 15% said they were concerned about the risks of adverse effects or the unevaluated efficacy of off-label drugs or issues of informed consent.

Studies conducted among parents found that their general awareness of off-label prescribing ranged between 14 – 35%. Parents generally believed that the majority of drugs prescribed for children in hospitals or in primary care settings had gone through the same testing and licensing procedures as those for adults. Research indicates that the majority of the public, including parents who had children with chronic conditions, lack knowledge of off-label prescribing and become less trusting of prescribing if they understand a drug is off-label or are not informed of the practice.

Mukattash et al. (48) looked at the attitudes of one thousand adults towards off-label prescribing to children in Northern Ireland; 61% of the study participants were parents. The vast majority (86%) of adults were unaware of the practice of off-label prescribing and 92% felt they should be informed when it occurred, preferably by their doctors. Ninety percent (90%) felt that off-label medications would increase the extent of adverse effects. Forty percent (40%) said that they would ask their doctor to change their medicine to one that was licensed If they received a drug prescribed off-label.

The author found that knowing whether a drug was being prescribed off-label had profound effects on whether adults felt medications were safe for their children. Before the study, participants were aware of off-label prescribing but only 1.8% felt that the use of medicines in children could be unsafe; after being informed about off-label prescribing, 62.4% felt medicines for children could be unsafe (48).

Lenk (49) looked specifically at the attitudes of parents with children, both healthy and those with chronic kidney conditions, towards off-label prescribing in Germany. The knowledge of off-label prescribing was poor in both groups; only 28% of the parents with healthy children and 35% of the parents of children with chronic diseases were aware that drugs could be prescribed off-label. Knowing whether a drug was being prescribed off-label affected parental attitudes towards treatment. Fifteen percent (15%) said they would refuse treatment with an off-label drug even if no other options were available and 25% said that they would consider off-label use only in special circumstances.

All of these studies indicate that the public are concerned about the evidence and effectiveness of off-label prescribing and may be less trusting of prescribing if the drug is being used off-label. This finding is also reflected in a study of 447 adolescents in Japan who were being prescribed an antidepressant being prescribed off-label (50). When the adolescents or their parents were informed the drug was being prescribed off-label, 40% of the patients refused the prescription.

2.3.5 Assessing the Risks and Benefits of Drugs Prescribed Off-label

Health Canada's drug approval process is intended to protect the health of Canadians by assessing a drug's benefit to harm ratio. Despite limitations in the standard drug approval process as described by authors such as Lexchin (51), if a drug is being used for off-label indications, Health Canada has not evaluated its benefit to harm ratio unless it has specifically rejected the drug for a particular use. Without the information derived from the drug approval process, there is no clearly established way of assessing the benefits and potential harms of a drug prescribed off-label.

The overarching parameter in terms of assessing prescription drug benefits and harms is that the level of benefits should define the level of acceptable harms. For example, liver toxicity may be acceptable in a drug approved for cancer but would be unacceptable if it were used for acne. Some researchers and jurisdictions have recommended specific policy and clinical practice approaches that could be used to improve the efficacy and safety of off-label prescribing.

Aronson et al. (52) describe the broad factors for prescribers to consider when assessing the benefit to harm balance of any prescription drug, including those prescribed off-label. These factors can be measured in relation to the worst and best benefit to harm balance. They include the characteristics of the patient including their age, the seriousness of the health condition (from trivial to life-threatening), the level of evidence of the drug's benefits and information on the drug's adverse effects. The authors also describe some specific guidelines for prescribers to consider when evaluating the safety and efficacy of an off-label use. They are contingent on the prescriber knowing what the approved and unapproved indications of a drug are. These include:

1. the existence of a severe or life-threatening health condition;
2. the lack of an authorized treatment for this condition;
3. authorized treatments being unavailable or having failed repeatedly;
4. the off-label use being supported by strong scientific evidence in the literature;
5. patients being fully educated about the off-label use and having given informed consent by a clinician who is aware that the drug will be used off-label;
6. patients and physicians having a way of reporting adverse events and outcomes linked to off-label uses.

European case law has also recommended parameters for off-label prescribing. These recommend that drugs should only be prescribed off-label when no authorized drug is available to treat a condition, that there must be sufficient evidence to prove the drug's effectiveness and safety and that, prior to prescribing, the prescribers undertake a process of informed consent with patients (10).

The presence of high-quality, evidence-based research is a central component for assessing the risks and benefits of off-label prescribing. However, this evidence is not always available when off-label uses are considered. Higher quality forms of evidence consist of systematic reviews of clinical

trials followed by individual randomized clinical trials and lower quality forms are observational studies such as case-controlled and cohort studies (53 – 54).

Gazarian et al. (55) note that observational studies, although a lesser level of evidence, are useful in assessing drug safety within post-market surveillance studies where signals of adverse drug effects (ADEs) have already emerged over time. While the authors acknowledge that expert opinion is sometimes referenced as a source of evidence for off-label prescribing, they consider it to be a lower level of evidence and one that is variable in terms of quality and rigor.

Largent et al. (56) recommend a framework for the ethical prescribing of drugs for off-label uses that takes into account different types of off-label use and the quality of evidence available. This involves categorizing off-label drug use into four categories and defining the level of scrutiny needed. These categories are new drugs, drugs with novel off-label uses, drugs with known adverse effects and drugs that are high-cost. These drugs are then divided into their evidentiary categories, (supported, suppositional and investigational), based on the level and quality of evidence. These factors provide guidance on the level of caution required when an off-label use is considered. All of these approaches support the need to use a clear set of guidelines for measuring the risks and benefits of off-label uses prior to prescribing.

2.3.6 Influences on Physician Prescribing

According to Weda et al. (9), in a study of off-label prescribing in the European Community, a main reason why physicians prescribe drugs for off-label uses is due to medical need because there may be a lack of licensed medicinal products available for specific indications. There are also more treatment options available when off-label uses are considered.

Pharmaceutical company commercial interests and their use of drug detailers and other approaches to promote drugs are significant influences on physician prescribing in general (57 – 59). However, since domperidone is off-patent and has been sold as a generic drug for many years (60), commercial interests may play a less important role.

I was not able to find evidence that companies producing drugs in generic form are promoting domperidone indirectly. Profits for companies producing generic drugs could be significant because generic drug manufacturers may have lower research and development costs than companies selling patented drugs (61 – 62).

Thistlethwaite et al. (59) describe prescribing as a complicated decision-making process involving patient and doctor influences, some of which are qualitative in nature. Although he suggests that pharmaceutical detailing is not as prevalent as it was in the past, many physicians still rely on pharma funded products, such as medication guides or other company sponsored information, as their primary sources of information about medicines.

In semi-structured interviews with 107 General Practitioners (GPs) practising in the north-west of England, Prosser et al. (63) emphasized the importance of pharmaceutical representatives as a key influence on physician prescribing but suggest that most prescribing decisions are based on the consideration of multiple factors. These include the physician's assessment of the failure of previous treatments and the ADE profile of the drug. The influence of colleagues and patient requests were also primary influences. The author describes GPs as being ' . . . largely reactive and opportunistic recipients of new drug information, rarely reporting an active information search' (p.60).

Fickweiler and Urbach. (64), in a review of physicians' interactions with pharmaceutical sales representatives (PSRs), corroborates Prosser et al.'s conclusions on the influence of pharmaceutical companies on physician prescribing. The study was based on a review of the medical literature between 1992 and 2016. It found that interactions between pharmaceutical sales representatives were frequent and often contributed to irrational prescribing practices. Pharmaceutical company influence was often targeted to physicians who were on the lower end of the medical hierarchy. The most common gifts to physicians were free drug samples. The review found that most interactions led to a higher use by the physicians of the drugs sponsored by the company.

Research indicates that practice and belief patterns may influence the degree to which physicians prescribe drugs off-label. Eguale et al. (2) found that physicians who scored higher on an orientation to evidence-based practice scale rather than to clinical experience were less likely to prescribe drugs off-label. This scale measured the attributes of evidence and non-evidence-based practice (65).

Physician characteristics associated with off-label prescribing have also been documented in the research literature on the off-label prescribing of antibiotics. Gonzalez-Gonzalez et al. (66) found that physician fears about the impact of non-treatment, prescribing complacency *vis-à-vis* patients (including physician perceptions of patient expectations), and insufficient knowledge of drug indications by physicians were associated with a higher level of off-label prescribing of antibiotics.

2.4 Breastfeeding and Low Milk Supply

2.4.1 Breastfeeding Benefits, Prevalence and Early Cessation

There is a strong global and national consensus on the importance of exclusive breastfeeding for a minimum of six months, followed by an additional two years with complementary feedings because of the overwhelming advantages of breastfeeding for the health of infants and mothers. Health benefits for women and children are related to the duration and exclusivity of breastfeeding. As well as being a worldwide nutritional priority, breastfeeding is considered a basic human right (67).

In a recent comprehensive analysis of the benefits of breastfeeding in the Lancet (68), the authors reinforce the lifelong benefits of breastfeeding to women and children:

> ‘Children who breastfeed for longer periods have lower infectious morbidity and mortality, fewer dental malocclusions, and higher intelligence than those who are breastfed for shorter periods, or not breastfed. This inequality persists until later in life. Growing evidence also suggests that breastfeeding might protect against overweight and diabetes later in life . . . . It can prevent breast cancer, improve birth spacing, and might reduce a woman’s risk of diabetes and ovarian cancer’ (p.476).
>
> This analysis concludes that:
>
> ‘Findings from epidemiology and biology studies substantiate the fact that the decision to not breastfeed a child has major long-term effects on the health, nutrition, and development of the child and women’s health. Possibly, no other health behaviour can affect such varied outcomes in the two individuals who are involved: the mother and the child’ (64: p.485).

The National Maternity Experiences Survey (2006 – 2007) (69), conducted by Statistics Canada, examined singleton births among women 15 years of age or older between November 2005 and February 2006. This report indicated an average of 90% of all Canadian new mothers intended to breastfeed their infants. Over 90% of new mothers initiated breastfeeding but by the time their infants were three months old only 67.6% were breastfeeding to any degree and only half (51.7%) were breastfeeding exclusively. By six months, the rate of exclusive breastfeeding had dropped to an average of 14.4% for all Canadian women. Women in British Columbia had one of the highest rates of exclusive breastfeeding: 19.2% at six months. Canadian breastfeeding rates are similar to those in comparable countries but the rates are lower than have been reported in previous Canadian research, suggesting that there may be general declines in the rate of exclusive breastfeeding in Canada by the end of six months (69).

Research has identified multiple socio-demographic and other variables that are associated with breastfeeding cessation. The literature is somewhat inconclusive because of the focus of researchers on either administrative data or on self-reports from mothers. Despite this, there are clear indications that a mother’s belief that she lacks sufficient milk to feed her infant is a major reason for breastfeeding cessation.

Al-Sahib et al. (70), in a study of data from the Canadian Maternal Experiences Survey, found that variables such as higher education, living with a partner, lower pre-pregnancy weight, and being older were associated with exclusive breastfeeding at six months while smoking during pregnancy, having a caesarean-section and infant admission to the Neonatal Intensive Care Unit (NICU) were associated with early breastfeeding cessation. However, this study did not collect information on mothers’ stated reasons for early breastfeeding cessation.

Large scale national studies, conducted in the United States, indicate that concerns about low milk supply are a common reason why mothers stop breastfeeding early. In a study of breastfeeding cessation using results from the US National Infant Feeding Practice Study II, Li et al. (71) asked 1323 mothers to identify their reasons for stopping breastfeeding during the first year. The

frequency of 32 different reasons for cessation was assessed and some sociodemographic variables were considered. The two most frequent reasons that women cited for stopping breastfeeding at different points of time during the first year, were that their babies were not satisfied by breast milk alone (an average of 49.5% of women at all weaning ages) and that that they did not have enough milk (45.5%). According to the authors, 'When a mother does not have confidence that she is providing an adequate quality of milk for her infant, she is likely to stop breastfeeding regardless of her infant's age' (71: p.573).

Ahluwalia et al. (72) looked at 2000 – 2001 data from the Pregnancy Risk Assessment and Monitoring System which collects data on maternal behaviours and experiences during pregnancy from 31 states and New York City. A third of the women did not initiate breastfeeding; four percent (4%) stopped breastfeeding in the first week, 13% in the first month and 51% continued for over one month. Sore nipples and a belief they were not providing enough milk were the two most common reasons women provided for stopping breastfeeding. After one week, a perception of having LMS was the most common reason why women said they stopped breastfeeding.

A Canadian study reflects the findings from research conducted in the US on the reasons why mothers stop breastfeeding early. Research conducted among 500 mothers having singleton births at several health centres in Nova Scotia between January 1, 2008 to December 31, 2009 found that the inconvenience or fatigue associated with breastfeeding (22.6%) followed by concerns about milk supply (21.6%) were the most common reasons why women stopped breastfeeding (73). In this study, 73.6% of the women had stopped breastfeeding within the first six weeks after their baby's birth. Women who were under 25 years of age, were primiparous or resided in high income neighbourhoods were most like to cite problems with milk supply.

Gatti (74) conducted an international review of research on insufficient milk supply based on a review of the literature from 1996-2007. The review based its findings on twenty studies conducted in eight countries, including Canada. Findings from this review indicated that, for 35% of the women who stopped breastfeeding early, a concern about milk supply was the primary reason cited. The author concluded that perceived insufficient milk supply appears to be a global problem and contributes to early weaning and decreased breastfeeding exclusivity.

2.4.2 Description and Diagnosis of Low Milk Supply

Low milk supply (LMS), sometimes also called insufficient milk supply (IMS), is a perceived or physiologically based deficit of breast milk insufficient to meet an infant's needs for growth and development. There are two broad categories of insufficient milk supply. In many cases these categories are not discrete and may overlap.

Primary lactation insufficiency refers to limitations in milk supply related to physiological conditions experienced by the mother and/or infant. Secondary lactation insufficiency (or perceived

breast milk insufficiency) is primarily defined as a mother's perception that she does not have enough milk to satisfy her baby's needs. Perceived milk insufficiency can occur when the physiological processes of breastfeeding have been interrupted by external factors that affect milk supply. For example, a mother's interpretation of a baby's behaviour can reduce the level of breastfeeding and stimulation of the breast required for effective breast milk production. There are also many socio-cultural or related factors such as a mother's need to return to work or institutional factors that discourage breastfeeding that can affect the breastfeeding process, especially in the early weeks postpartum (75 – 78).

Gatti (74) notes that there is confusion related to the use of the terms perceived insufficient milk supply (PIMS) and insufficient milk supply (IMS) with both (or comparable descriptors) being poorly differentiated or being used interchangeably. Marasco (75) suggests that real or primary insufficient milk production often lacks formal diagnostic criteria but that this term and diagnosis are commonly used when normal breastfeeding management methods fail to address problems with milk supply and where there is no clear physiological barrier to breastfeeding. The author believes that the lack of differentiation of these two types of insufficient milk supply is a clear limitation of the research because they ultimately have different causes that require different interventions.

There are many physiological factors that can be associated with primary milk insufficiency. One of the most common is mammary hypoplasia or a lack of sufficient glandular tissue, sometimes resulting from existing conditions or due to breast reduction surgery. In a study of lactation sufficiency in a cohort of women, Neifert et al. (78) found that women with periareolar breast incisions were five times more likely to have milk insufficiency than those without surgery.

Other physiological conditions that may be associated with lactation problems related to the mother are endocrine problems, severe illnesses including infections, postpartum hemorrhage, and conditions such as mastitis, spinal cord injuries, obesity, thyroid dysfunction and hypertension (75 – 78). Marasco (75) notes that there is a lack of definitive research on many potential causes and contributors to insufficient milk supply including the role of polycystic ovarian syndrome, hypertension, the role of prolactin, the influence of endocrine disruptors in the environment, infertility, metabolic disorders such as diabetes and advanced maternal age.

Despite the association of some of these conditions with LMS, there is a lack of research on how they ultimately affect breastfeeding. As stated by Neifert et al. (78), 'the contribution of factors such as the influence of breast surgery, breast appearance and pregnancy induced breast changes do not represent absolute contraindications to breastfeeding' nor should any be cited prenatally to portend failure' (78: p. 37). Infants can also have conditions that affect their ability to breastfeed effectively. These can include facial abnormalities such as cleft lip or cleft hard or soft palate, tongue-tie, and sucking impairments related to varying causes such as muscle tone issues, cardiac defects or metabolic disorders (76).

The incidence of primary milk insufficiency is thought to be low, but because of the variability of effects there is no definitive data on the prevalence of breastfeeding mothers who cannot breastfeed due to physiological factors. In Neifert et al.'s study of 319 healthy primiparous women who were breastfeeding, at three weeks postpartum, 15% had persistent milk insufficiency despite intensive interventions; 6.9% of the study population had undergone previous breast surgery and this factor was significantly correlated with lactation outcomes. Other estimates of primary milk insufficiency range from 1 – 5% (78).

Secondary breast milk insufficiency or perceived breast milk insufficiency is the most common type of low breast milk supply and is the focus of my research. None of the mothers included in my interviews had physiological conditions that limited their milk supply although several were initially told they did. The term 'low milk supply' when used in this research refers primarily to secondary causes that are unlikely to be caused by physiological conditions that affect milk supply. However, as noted above, primary and secondary causes of LMS are not always delineated.

The most validated method to objectively measure a mother's milk production is test/retest weighing of a baby before and after being breastfed to measure breastmilk volume over a 24-hour period (79). This method is used to assess whether a mother has adequate breastmilk supply to feed her infant. The degree to which test and retest of breast milk volume is undertaken over a 24-hour period is unknown. Mannion and Mansell (80) suggest that, 'Maternal perception of insufficient milk production is almost never validated by measured milk volume but is a prime influence in maternal decision-making to supplement with formula, discontinue breastfeeding, or use products that stimulate milk supply' (p.2, 3).

However, researchers have identified limitations of this milk volume measuring method. The amount of breast milk taken in by a baby may vary from feed to feed. If only one or two test/retest weightings are completed in a day that indicate low milk volume, the results may be misinterpreted as indicating LMS rather than being an infant's normal feeding pattern. Undertaking pre- and post-feed weighing of the baby may be anxiety-producing for a new breastfeeding mother if done in a clinician's office or in front of a clinician and this may negatively affect the mother's milk ejection reflex resulting in lower milk production. The measurement of milk volume may also contribute to the medicalization of breastfeeding by quantifying milk production for the mother and clinician.

In many cases, healthcare providers assess milk supply using observational or qualitative measures. These include counting the number of wet diapers and stools per day to assess the infant's level of hydration and observing the infant's alertness, skin tone and the level of weight gain particularly in the first few weeks postpartum (81, 82).

Healthcare providers may rely on a mother's reports of having insufficient breastmilk as indicating an inadequate milk supply. However, in a Canadian study of 123 breastfeeding mothers,

Galipeau et al. (77) found that maternal perceptions of insufficient milk supply were not always associated with insufficient milk supply when this was measured by a baby's weight loss or of a mother's 24-hour production of breast milk.

2.4.3 Factors Associated with Perceived Low Milk Supply

Research suggests that there are a number of key factors that can contribute to a mother perceiving that she has LMS. These can include a mother's personal perceptions and lack of knowledge of infant behavioural cues and the lactation process, her level of confidence and breastfeeding self-efficacy and institutional (hospital based) policies or practices that may act as barriers to effective breastfeeding. Other factors include the impacts of healthcare providers on breastfeeding mothers including their perceptions about normal infant weight gain patterns after birth and how and when they make a diagnosis of LMS. There is a lack of data on whether and to what degree these multiple factors interact in order to affect a mother's concerns about low milk supply.

As noted by Kent et al. (81), mothers will perceive their breastfeeding to be normal or abnormal according to their expectations of normal breastfeeding. Research suggests that some mothers may not be sufficiently knowledgeable about normal lactation or how to interpret infant behavioural cues which can lead them to interpret common behaviours such as fussiness or sleepiness as indicating a lack of satiety. The misinterpretation of baby cues may lead to a mother believing that she has LMS (71, 74, 81 – 83).

According to Gatti (74), misconstruing an infant's behaviour as hunger is a common reason for assuming LMS. She states that the literature on LMS,

> ' . . . indicates that most women use infant satisfaction as their major indication of milk supply. Many women perceive crying, fussiness, and wakefulness as signs that their infant is not receiving enough milk. While these signs may be part of an infant's feeding cues, they can also be normal infant behaviour, and may vary as infant temperaments vary' (p.362).

Hookway (83) states that some mothers believe that their infants may settle more easily after receiving formula. They then may interpret this to mean that their milk supply has been inadequate. However, the author notes that when babies drink formula they may overfeed and as a result may fall asleep more easily after a feeding. In her view this is because the baby needs to digest larger volumes of milk which are likely to be physiologically abnormal compared to the milk from breastfeeding and that may not be appropriate in terms of the infant's needs and capacity. A mother's accurate interpretation of infant satiety is important because if a mother perceives that her baby is satisfied by her own breast milk this enhances her confidence and self-efficacy (77, 81).

A mother's misinterpretation of baby cues and behaviour may be related to her lack of knowledge of the stages of lactogenesis, the supply-demand relationship of effective breastfeeding, or how a baby expresses its needs through patterns of sleep and feeding. Newborn babies need to feed

frequently – sometimes ten to twelve times a day and are likely to feed at night for at least six months. The length of time a baby feeds is variable and ranges from 12 to 67 minutes. Not all of this time is spent breastfeeding. After the first few weeks, a woman's breasts will feel less full and she may feel her milk supply is decreasing but this is not the case. The volume of breast milk remains relatively constant after the establishment of a mature milk supply at six weeks, until six months (81 – 84).

Mothers may also lack information on how well babies are adapted to the early postpartum period when only small amounts of colostrum are available. Galipeau et al. (77) suggest that, although frequency of breast stimulation is essential to milk production in the early weeks postpartum, mothers in their study often expressed difficulty in determining how often they should breastfeed. When they observed changes in their breasts after a few weeks postpartum they sometimes interpreted this as their milk drying up rather than as an indicator of established milk production.

These types of information gaps about lactation may be exacerbated by a mother's lack of access to practical, accurate and consistent information and support about breastfeeding. Research suggests that a variety of non-pharmacologic methods can support both breastfeeding exclusivity and duration. One systematic review looked at the impact of a range of types of professional and lay support in terms of supporting women to exclusively breastfeed. Supportive interventions included in the systematic review were highly diverse and included reassurance, praise, information, the opportunity to discuss issues, staff training, one-to-one and group sessions in the hospital or in the community. The review included 52 randomized control trials from 21 countries that included more than 56,451 women. All forms of support were associated with an increase in the time women breastfed and the length of time before solids were introduced. Face-to-face support was found to be more effective than telephone support (85).

Leurer et al. (73) undertook a qualitative analysis of the specific information gaps experienced by breastfeeding mothers. The major gaps identified in the study included a lack of clarity on feeding frequency and length, more guidance on reading baby's cues, reassurance that their baby was getting enough milk or ways of assessing their milk supply, information on correct latch and feeding positions, more information on expression and pumping, nipple care, and more realistic information in response to breastfeeding concerns.

Lewallen et al. (86) looked at the reasons why mothers stopped breastfeeding in the first eight weeks postpartum and whether these reasons were amenable to nursing education and support. The study included 399 women with 379 being able to be contacted at 8 weeks postpartum. Of the 121 mothers who had stopped breastfeeding by eight weeks postpartum, the major reason cited, by 34.7% of this group, was having insufficient milk supply. She noted that 92% of the 379 participants said they received information and support while at the hospital, but this support dropped to only 54.8% after the mothers left the hospital. The author contends that later postpartum support may be more essential to address breastfeeding problems, in that breastfeeding classes provided prior to

delivery and just after birth focus on the benefits of breastfeeding and getting started but that 'many people need additional information after delivery in order to tell if they are getting enough milk from the breast' (86: p.170).

2.4.4 The Impact of Institutional Policies on Low Milk Supply

Institutional policies and factors can affect the early establishment of milk supply. Policies that support early initiation of breastfeeding, encouragement of regular breastfeeding, skin-to skin contact between mothers and babies and rooming in are known to support the early establishment of breastfeeding. (76, 81, 82, 84, 85, 86, 87). In a systematic review, Moore et al. (87) explored the impact that early skin-to-skin contact had on breastfeeding duration. Results indicated that mothers who had early skin-to-skin contact with their babies were more likely to breastfeed one to four months longer than mothers who experienced mother-baby post birth contact that involved physical separation.

A breakdown in the establishment of early breastfeeding leading to a mother's perception that her milk supply is inadequate can contribute to her being encouraged to accept early hospital-led supplementation with water and formula for her infant. This can further affect the establishment of effective lactogenesis by disrupting the intensive sucking of the baby on the breast which is essential for milk production. When this is disrupted it can lead to a downward spiral in terms of milk supply, which some mothers find difficult to reverse:

> 'Suboptimal hospital policies may also restrict the length of frequency of feedings in the early postpartum period or have policies such as visiting hours that may restrict the opportunity of mothers to breastfeed often in the first few days postpartum. The family may then interpret their baby's normal desire to feed longer or more frequently as a sign that the colostrum is not enough for the baby, leading to supplementation' (76: p.6).

2.4.5 The Importance of Breastfeeding Self-efficacy

Self-efficacy, when used in the context of breastfeeding, describes the degree of confidence a mother has in her ability to breastfeed. According to Bandura (88), who developed a commonly used theoretical construct for self-efficacy, the concept involves both outcome expectancy, which is the belief by a person that a behaviour can produce a specific outcome, and self-efficacy expectancy – the belief that a person can complete the tasks essential for this outcome.

Bandura hypothesized that expectations of personal efficacy 'determine whether coping behavior will be initiated, how much effort will be expended and how long it will be sustained in the face of obstacles and aversive experiences' (p.191). He postulated that self-efficacy is derived from four sources of information: performance accomplishments, vicarious experiences, verbal persuasion and emotional arousal. Elements of Bandura's model or related models have been applied to breastfeeding efficacy which is considered to be influenced by a multiplicity of factors including a mother's previous breastfeeding experience, encouragement and support provided by others,

including healthcare providers, seeing others breastfeed successfully, the emotional/psychological state of the mother including her level of fatigue, self-doubt, depression and anxiety and her interactions with her baby (89, 90).

The Breast-Feeding Self-Efficacy (BSE) short form is an example of one validated 14-item form that is widely used to measure the degree to which a mother feels confidence about her breastfeeding (89). Results from the breastfeeding literature indicate that maternal confidence in the ability to breastfeed is associated with the duration of breastfeeding. Some research suggests that there is an association between the level of a mother's sense of self-efficacy and the degree to which she believes her milk supply is adequate (77).

In a Cochrane systematic review of the literature on the effectiveness of interventions to support breastfeeding self-efficacy and the degree to which BSE improved breastfeeding rates, Brockway (90) found that in seven out of 11 studies, education to promote self-efficacy in breastfeeding led to higher self-efficacy rates in the intervention group. Almost half of the studies reported associations between breastfeeding self-efficacy and a higher prevalence of breastfeeding. Educational interventions that were most successful in predicting improvements in breastfeeding self-efficacy and that led to higher rates of exclusive breastfeeding were implemented in the postpartum period, used combined delivery settings and were based on the theory of breastfeeding self-efficacy. However, the authors noted that seven studies in the review were of low quality and only four studies had single blinded outcome assessors.

In a study of a cohort of 18 – 34-year-old mothers over six months which looked at the association of self-efficacy, perception of milk production and use of medications to increase milk supply in a Canadian setting, Mannion and Mansell (80) found that women who scored lower on a breast-feeding self-efficacy short form scale were more likely to use formula or a prescription drug, (in this study it was domperidone), to increase their milk supply. Several studies explored the association between the mother's level of self-efficacy and perceptions about the adequacy of her milk supply. McCarter-Spaulding (91) found that mothers who reported more confidence in parenting an infant were less likely to believe that they had LMS.

A systematic review and meta-analysis of the breastfeeding literature by Galipeau et al. (92) assessed the efficacy of interventions to support BSE and looked at whether BSE was associated with maternal perceptions of insufficient milk supply. Seventeen (17) studies were included in the analysis with 12 being randomized control trials (RCTs). The results of the systematic review indicated significantly improved self-efficacy after educational interventions during the first four to six weeks. However, the meta-analysis did not show any effect on breastfeeding cessation during this period despite improvements in maternal BSE. The authors indicate that more research needs to be undertaken on the best interventions to support self-efficacy and how self-efficacy relates to concerns about breast milk sufficiency.

In a separate study of the breastfeeding experiences of 213 mothers at a Canadian hospital, Galipeau et al. (77) found that women who scored higher on a self-efficacy short form were more likely to assess their milk supply as sufficient. Otsuka et al. (93), in a cross-sectional study of 262 breastfeeding mothers who had in-hospital births in Japan, looked at the association between breast-feeding self-efficacy, exclusive breastfeeding and the degree to which perceived insufficient milk supply was associated with breastfeeding cessation. The subjects completed both a breastfeeding self-efficacy short form and a questionnaire asking about perceived insufficient milk supply and infant feeding methods at four weeks postpartum. The majority (82%) of participants intended to exclusively breastfeed, however, only 40% were doing so at four weeks postpartum. Mothers who reported higher levels of breastfeeding self-efficacy at hospital discharge had lower perceptions of insufficient milk at four weeks postpartum. However, the authors conclude more research is needed to test these associations saying that, 'while there is general consensus that self-efficacy and confidence support breastfeeding duration, there are gaps in the literature in terms of the association between self-efficacy and perceptions of insufficient milk supply' (93: p.552 – 553).

2.4.6 Expectations of Baby's Early Weight Gain

A primary measure of the adequacy of the breast milk supply in the first two weeks postpartum is the amount of infant weight loss after birth, the level of weight gained in the first few weeks and how long it takes for the infant to regain this birthweight. To determine this, an infant is routinely weighed after birth, at hospital discharge and at additional times in the hospital and in the community by various healthcare providers including nurses, midwives, physicians or lactation consultants.

I was unable to determine the exact process for monitoring milk supply when a baby is born at home or in a birth centre. However, midwives frequently attend these births and provide breastfeeding support including the monitoring of a mother's milk supply for the first few weeks postpartum. Community nurses and lactation consultants provide services to breastfeeding mothers where they are available.

All babies lose a percentage of their body weight after birth. Research indicates that breastfed babies initially lose more weight and take longer to regain it than formula-fed babies (94, 95). Most babies lose their highest percentage of body weight at about 3 – 4 days postpartum before beginning to regain their birth weight within approximately two weeks.

During the first few days postpartum, breastfed babies are reliant on small amounts of colostrum from the breast which contains proteins with immune functions. Tawia and McGuire (96) describe how healthy, full-term, exclusively breastfed babies are well adapted to survive on the fluid and energy reserves in their bodies during this period, saying that, 'These homeostatic processes are the physiological norm and exist to maintain newborn infant water, glucose, and energy levels-vital requirements-until large volumes of milk are available' (p.35).

Guidelines that have defined the parameters for acceptable infant weight loss and the time needed to regain birthweight have been developed by a range of professional organizations, however, the advice given in these guidelines has sometimes been contradictory. In a discussion of guidelines from four established breastfeeding organizations, including the Academy of Breastfeeding Medicine and the International Lactation Consultant's Association, Grossman (94) and Tawia and McGuire (96) found professional guidelines to be variable. Guidelines for the maximum amount of weight to be lost ranged between 7 – 10% of the infant's body weight and other conflicting advice was also included. As noted by Grossman, 'these guidelines do not address timing of weight loss, nor do they take into account other factors that can affect infant weight loss, such as type of delivery or maternal fluids in labour' (94: p.410).

Research also suggests that there is no clear consensus on the weight loss patterns of newborns in the first few days of life (95 – 98). There is also wide variability in the time it takes some infants to regain their lost weight (95, 97, 98), in some cases as long as three weeks.

In a review of the literature on physiological weight loss in the breastfed neonate, Noel-Weiss et al. (97) attempted to determine the parameters for normal weight loss for a full-term breastfed infant in its first two weeks and the appropriate time for triggering interventions. She concluded that there was insufficient data to accurately answer these questions due to the limitations of the research. These limitations included inconsistencies in the measuring of the baby's weight and inadequate reporting of drop-outs in research reports. In their conclusions, the authors oppose using an absolute number to establish weight gain expectations because they do not take individual ranges and standard deviations into account. The authors conclude that,

> ' . . . when distinguishing a physiological from a pathological weight loss, an absolute number may cause health professionals to miss red flags. For example, a 3-day old infant with a 7-10% weight loss is probably reaching his or her lowest weight before gaining, and this child would be in a different situation than a 9-day old infant who weighs 10% less than his birthweight. Not only has the 9-day old infant lost weight, but he or she has not regained and is therefore further behind than the 3-day old infant' (97: p.E20).

Extreme levels of weight loss and slow regaining of birthweight are of concern in the first weeks after birth because they can be indicators of more serious health problems. The most common of these is hypernatremic dehydration (99, 100) which is a high concentration of sodium in the body due to fluid loss. In a systematic review of the treatment of hypernatremia, Bischoff et al. (99) found that weight loss in excess of 10% of birthweight occurs in 15% of breastfed infants and about one-third of these will have some clinical signs of dehydration.

In a prospective study of healthy term and near-term babies over five years, Moritz et al. (100) found that the incidence of pediatric hypernatremia was 1.9%, with jaundice being the most commonly presenting symptom. Mean weight loss was 13.7%. The condition appears to be relatively common

and, although potentially serious, is easily addressed when diagnosed early. Severe complications appear to be rare.

Research has established that the monitoring of weight loss and the use of narrow guidelines about maximum weight loss can contribute to the early introduction of formula and may contribute to early breastfeeding cessation. In a study of weight changes in full-term breastfeeding newborns during the first two weeks of life, DiTomasso and Paiva (98) found that 56% of the infants in the study lost over 7% of their bodyweight. In this group the use of formula increased markedly by 14 days in comparison to the babies who lost under 7% of their bodyweight. Verd et al. (101) found that in cases where weight loss was above the median (6%), breastfeeding was more likely to be discontinued at 15, 30, or 100 days postpartum.

DiTomasso and Pavia (98) and Verd et al. (101) believe that close weight loss monitoring may contribute to early breastfeeding cessation. As noted by DiTomasso and Pavia:

> 'When a provider expresses a concern about a newborn's weight loss, this has the potential to shake a woman's confidence in her ability to breastfeed. Women who lack confidence are then more likely to discontinue breastfeeding and/or supplement with formula' (p.91).

2.5 The Influence of Medicalization on Breastfeeding

Childbirth and breastfeeding have become increasingly medicalized (102 – 105). The influence of medicalization on breastfeeding and perceptions of breastfeeding problems, including LMS, is included as an area of analysis in my social-ecological model at Level 5 under socio-cultural factors (Figure 1).

Medicalization is defined as 'the process by which some aspects of human life come to be considered as medical problems, whereas before they were not considered pathological' (102: p.1). The drivers of medicalization include the commodification of health for consumers, the growing use of diagnostic tools so that the definition of risks requiring treatment are expanded, and by the promotion of medical management and control for health problems (106).

Abraham (107) has also described the pervasive use of pharmaceuticals in medicine and society as a specific category of medicalization that he labels the 'pharmaceuticalization' of health that he defines as 'The process by which social, behavioural or bodily conditions are treated or deemed to be in need of treatment/intervention with pharmaceuticals by doctors, patients or both' (p.290). The author believes that that broader social trends such as the political economy of the pharmaceutical industry and industry promotion of prescription drugs help shape patient self-diagnosis leading to demands for medications.

Torres (103) has explored aspects of medicalization specifically related to breastfeeding through a discussion and analysis of the experiences of lactation consultants. Lactation consultants are professional licensed healthcare providers who play a primary role in advising mothers about

breastfeeding. The author identifies four dimensions that she believes contribute significantly to the medicalization of breastfeeding. These are:

1. The extent to which breastfeeding problems are defined in medical terms. This relates to the construction of breast milk as a medical product with a stress on its nutritional properties rather than on the process of breastfeeding which focuses on the relationship dynamic between the breastfeeding mother and baby.
2. The increasing medical surveillance and control of breastfeeding as evidenced by a growing use of 'specialists' who 'manage' breastfeeding and who generally reinforce a medical approach. This trend towards medical management reflects the growth of 'scientific motherhood' which appeared in the 20th century. It stressed that women need the scientific and medical advice of experts in order to raise healthy children.
3. The extent to which the breastfeeding process or breastfeeding concerns are 'pathologized or constructed as abnormal or prone to disorder' (103: p.161). This dimension revolves around issues such as the health and purity of breast milk, the mother's behaviour while breastfeeding, her ability to produce a sufficient quantity of milk and the degree to which breastfeeding is seen as a normal physiological process or a potential failure of a woman's body.
4. A focus on the use of medical treatment, particularly the use of technologies, to address breastfeeding problems. The primary technology used to address breastfeeding problems is infant formula but other technologies noted by the author include breast pumps, nipple shields, feeding syringes and pharmaceuticals.

In a discussion of the medicalization of birthing experiences, Brubaker et al. (102) concluded that the medical model is the 'master narrative' for women's reproductive experiences and is based on a medical authority's usurpation of (a woman's) authority, choice and control over her reproduction requiring her 'to consult medical experts for what has traditionally been a woman's domain' (p.35). Although this paper focuses primarily on experiences related to childbirth in hospitals, for the vast majority of women, the early phase of breastfeeding begins within hospital and under the control of a medical institution and medical personnel/managers. The paper does not discuss the experiences of medicalization in women who give birth at home or in birth centres but, in many cases, these births are attended and followed by midwives who also espouse types of medical management of breastfeeding in similar ways to lactation consultants.

Torres (103) discusses the contradictory role of lactation consultants who, while they attempt to support demedicalization, also medicalize breastfeeding as a result of their position as medical authorities and their reliance on medical terminology and technology.

The consideration of breast milk as a product rather than as emanating from a normal physiological process based on the reciprocal and dynamic relationship between mother and baby has

been explored by Penny Van Esterik (108), a Canadian anthropologist whose research has focused on understanding multicultural breastfeeding beliefs and practices. She describes a shift from the interpretation of breastfeeding as a natural process to that of supplying a (milk) product and notes that, 'Process models emphasize the continuity between pregnancy, birth and the process of lactation. The biochemical model with its accumulated evidence about the nutrient content of breast milk and breast milk substitutes is a product-oriented model' (p.5).

In additional research, Van Esterik (109), notes that reducing breast milk to its nutritional content underestimates the importance of the reciprocal relationship that occurs between mother and baby during breastfeeding which is based on nurturance and the growing agency of the baby. According to the author, 'The embodied co-dependence of the breastfeeding mother and infant intensifies this 'personing' process. Breastfeeding teaches a newborn how to build and maintain an emotionally charged relationship with mother or another caregiver' (p.1).

The use of breast pumps in conjunction with the detailed visual measurement of breast milk volume so that mothers can see the extent of their supply, reflects aspects of the medicalization of breastfeeding and reinforces the view of breast milk as a product.

An increasing number of women routinely use breast pumps to extract breast milk which can then be fed to their babies in a bottle. Using data from the US 2005 – 2007 Infant Feeding Practices Study, Rasmussen and Geraghty (110) found that 85% of breastfeeding mothers of infants expressed their milk and most did this routinely using breast pumps; 5.6% of the mothers exclusively pumped milk to feed their babies and never fed their babies from the breast. (p.1356). Torres (103) also views breast pumps as playing a significant role in the medical management of breastfeeding because they allow 'the lactation consultants (and the mothers) to quantify and track how much milk is being produced, as well as set goals for milk production' (p.164).

Early and regular breastmilk pumping has been associated with early breastfeeding cessation. Yourkavitch et al. (111), using data from the Infant Feeding Practices Survey II, found that non-working mothers who pumped regularly were more than twice as likely to stop breastfeeding as non-regular or non breast milk pumpers. Torres (103) also notes that the measurement and management of breastfeeding, as reflected in the collection of pre- and post-feeding weights, often requiring the measurement of an infant's weight in tiny increments, strongly reinforces aspects of medicalization and may lead to mothers losing confidence in their milk supply.

New technologies, available to breastfeeding mothers also encourage the medical management of breastfeeding. In the past few years, devices that mothers themselves can use to quantify the amount of milk their babies are receiving have been developed and promoted. Momsense (112) is a smart breastfeeding meter that analyzes a baby's swallows through a microphone placed by the baby's jaw and then reports out detailed data on a mobile device app which is on the mother's

smart phone. The mother can then access real time data on the amount of milk her breasts are producing during the breastfeeding session.

Sanja Nel, a lactation consultant, who provides support to breastfeeding mothers on her website (113), believes that tracking the amount of breast milk consumed by a baby using these devices may not be accurate because they cannot take into account the unique needs and nursing patterns of infants. She is also alarmed at the anxiety-producing messages these measuring products send directly to mothers at the time when they are nursing. She believes that these devices send the message to mothers that,

> ' . . . your instincts are not good enough and that your body is unreliable; you cannot possibly raise a baby without some high-tech help (at a price, of course). It's preying on women's insecurity and anxiety about wanting to give their babies the best. It tries to convince you that you're no good at reading your baby's cues; that you should rather put your trust in technology . . . . I firmly believe that learning to read your baby's cues is one of the most important things that breastfeeding teaches you, and that it's part of the reason why breastfeeding mothers develop such a strong bond with their babies. Learning to read your baby will serve you well for the rest of your time as a parent, so rather than spending your time adding up numbers and analyzing figures, just concentrate on getting to know this new little person in your life' (113: pe.1).

Torres (103) describes infant formula as the major technology reflecting the medicalized management of breastfeeding. Wallace and Chason (105) describe how medicalization is extended by formula manufacturers into breastfeeding settings, saying that this is,

> ' . . . further evidenced by, and reinforced through, the influence and massive presence of formula manufacturers in health care settings. Institutionalized distribution of artificial feeding products, provided to hospitals and physicians by pharmaceutical companies to distribute at hospitals and medical offices, appears to be another avenue by which mainstream medical care works against natural feeding' (p.410).

Formula feeding is pervasive. A recent international report on the formula industry by Save the Children UK (114) described the global formula market as being projected to be worth more than US 70 billion dollars in 2019; this was a 5-fold increase in two decades. Most of the growth in this industry is due to powerful marketing campaigns by six international companies that have resulted in mothers giving up or reducing breastfeeding, despite negative health consequences for both babies and mothers. As the authors note:

> 'The decline in breastfeeding has been linked to Western epidemics of inflammatory disease and obesity, and has the potential to affect the health of future generations. And yet manufacturers of milk formulas – a direct competitor of breast milk – have successfully established a supposed 'equivalence' in the minds of many people between breast milk and milk formula, creating the perception that the latter is simply an artificial replica of the former' (114: p.v).

In addition, the massive budgets spent by formula companies to promote their product dwarfs the amount that public health budgets have the capacity to spend promoting breastfeeding or hiring public health staff to provide support and education to breastfeeding mothers.

Torres (103) believes that formula reinforces the view that breast milk is a medical product separated from the process of breastfeeding:

> 'Not only do these technologies play a crucial role in the medical management of breastfeeding, but they also reinforce the definition of breast milk as a medical product. In the case of breast pumps, the product is literally separated from the process of breastfeeding' (p.164).

She contends that focusing on breastfeeding as a means of delivering a product (breast milk), rather than as part of a natural human process, has led to breastfeeding being considered a moral imperative for mothers and part of their duty to reduce every risk to their children, even to their own detriment.

Medicalization also ignores many of the social, structural and cultural barriers that many women face while attempting to breastfeed. Maturo et al. (106) state that another aspect of medicalization is that it 'reponsibilizes' patients or citizens for their own health problems, rather than taking into account the social determinants such as class and poverty that may affect individual health choices such as breastfeeding. Wallace and Chason (105) also suggest that infant feeding practices reflect the social position of women and the increasing social control of knowledge and practices by medical and pharmaceutical institutions. Breastfeeding is seen as simply one alternative among many rather than a universal experience for women.

Moynihan at al. (115) provide a different perspective on the medicalization of health conditions that is also relevant to breastfeeding and mothers' perceptions of having LMS. The authors describe the process of over-diagnosis as an important component of medicalization. This occurs when those with mild or no serious symptoms of a health problem are medicalized, diagnosed and labelled with a condition that may cause them to be classified as sick which then leads to overtreatment, including the overuse of pharmaceuticals. In their view, a key contributor to over-diagnosis is technology, which commonly includes sensitive measuring and testing to broaden the scope of a condition.

2.6 Characteristics, Use, Efficacy and Safety of Domperidone

2.6.1 Characteristics and Use of Domperidone

Domperidone is a dopamine D2-receptor antagonist which has been approved for use in Canada as an antiemetic to prevent nausea and vomiting and as a prokinetic to enhance gastric motility and relieve gastrointestinal symptoms such as nausea, vomiting and heartburn. It does this by inhibiting the dopamine receptors in the human gut (116 – 118).

Domperidone was approved in the US for dyspepsia in 1978, prior to some of its adverse cardiac effects being well recognized. Hondeghem (119) concluded that studies on the benefits of domperidone for these gastrointestinal indications were inconclusive and that trials were limited in size and study design. In 1986, the intravenous use of the drug was withdrawn in the US and the drug is

available there now in any form only through special access provisions, (120) although it may be acquired online in tablet form from Canadian pharmacies with a prescription.

In Canada, domperidone was initially marketed under the brand name Motilium by Janssen Pharmaceutica in 1990 and is now sold by various companies in a generic tablet version. It has never been approved to treat low breast milk supply in Canada or in any other jurisdiction, so all of its use for this indication is off-label.

One of domperidone's actions is the elevation of serum prolactin levels which can lead to unintended lactation among those taking the drug (116). For this reason, it has been increasingly prescribed in some jurisdictions off-label to breastfeeding mothers to treat low breast milk supply. Research conducted in BC indicates that the prescribing of domperidone to breastfeeding mothers increased dramatically between 2002 and 2011 and by 2011 involved one in five mothers of full-term babies and one in three mothers of preterm babies (1).

Domperidone is also described as a 'hidden' neuroleptic related to other neuroleptics, such as risperidone (121), which have side effects such as akathisia, restlessness, and depression due to its blockage of D2 receptors which not only affect the gut but also the central nervous system. It was thought that the blood-brain barrier would be protective against domperidone's affects on the central nervous system but research now indicates that dose levels between 30 mg and 160 mg per day could lead to the drug acting as an anti-psychotic exposing patients to many adverse effects, including effects upon withdrawal from the drug (119).

Domperidone also can precipitate long QT syndrome, an electrical disorder of the heart which can expose patients to the risk of cardiac arrhythmias which can be fatal (119,121 – 122). This is the most serious harm associated with the use of domperidone and is described in more detail in Section 2.6.2.

Domperidone is widely prescribed in Canada with approximately 2,000,000 prescriptions reported by Health Canada in 2013 (122). However, the degree to which these prescriptions are off-label and used to treat LMS has not been precisely determined because the prevalence of off-label prescribing is not tracked nationally.

There is a lack of published research on the prevalence and use of domperidone in the postpartum period or to specifically address low milk supply. The only Canadian study exploring the prevalence of domperidone use to treat low breast milk supply on a broad scale was completed in BC in 2016 (1). This study, which included all women with a live birth in BC between Jan 1, 2002 and December 30, 2011, found that the prevalence of domperidone prescribing more than doubled between 2002 and 2011, growing from 8% to 19% among women with term births and from 17% to 32% for women with preterm births. The size of domperidone dose levels and the duration of prescriptions also increased during this period. For the initial prescription, the median daily dose

increased from 60 mg in 2002 to 80 mg in 2011. There was a rise in the dose levels of prescriptions with doses greater than 80 mg/d growing from 11% in 2002 to 19% in 2011. Median duration for drug treatment was 21 days in 2002 but 30 days in 2011. Ninety-two percent (92%) of prescribing was done by general practitioners and 86% of the mothers had term births.

A much more limited study, suggesting the prevalence of domperidone use in breastfeeding mothers, involved a convenience sample of 76 mothers who attended a parent drop-in at a Community Health Centre for breastfeeding support in Calgary, Alberta. Twenty-eight percent (28%) of these mothers used domperidone. The rates of exclusive breastfeeding among this group were low (80).

Mehrabadi et al. (123) looked at the trends in the prescribing of domperidone to treat low breast milk supply in England. This interrupted time series analysis also focused on the potential impact of a 2014 European Medicines Safety Agency recommendation to restrict the drug's use because of concerns about its cardiac safety (124). The cohort studied by Mehrabadi et al. was women, 15 – 45 years of age, with live births between May 1, 2002 and March 31, 2015. The study found that domperidone to address lactation problems was not widely prescribed in England (rate of 1.24 per 100 person years) but that the rate of use increased from 0.56 to 2.1 per 100 person-years between 2002 – 2004 and 2011 – 2013. There was a non-significant decrease in the level of prescribing immediately following the recommendation to restrict the drug's use. There was also a trend towards prescribing domperidone earlier in the postpartum period as well as prescribing higher doses of the drug.

The authors posed the question of why prescribing rates for domperidone in England are so much lower than those indicated in the Canadian research and posed some possible explanations:

> 'It is unclear why postpartum domperidone use is extremely high in Canada as compared with England. Canadian prescribing practices may have been influenced by Canadians leading clinical trials on domperidone use and many Canadian expert leaders and organizations that have been proponents of domperidone use' (123: p.1323).

Examples of proponents in Canada who recommend the off-label use of domperidone to treat LMS include the authors associated with a paper by Bozzo et al. (125) and with a consensus statement authored by Flanders et al. (126). The authors associated with these documents support the use of domperidone to treat low milk supply, sometimes at doses substantially over the 30 mg/day recommended by Health Canada and the European Medicines Agency (122, 124).

A 'Consensus Statement on the Use of Domperidone to Support Lactation' (126) was endorsed by a group of breastfeeding experts and researchers on breastfeeding and was co-authored by Dr. Jack Newman who runs a breastfeeding support and information site. Dr. Newman often suggests doses of domperidone over 80 mg/day when there is a lack of response to lower doses. The statement reviews the profile of domperidone and its contraindications and does suggest that it should

not be used by those with underlying cardiac problems. However, it concludes with the following commentary about the Health Canada 2015 warning (127) on domperidone:

> 'In summary, breastfeeding mothers using domperidone do not fall into the same demographics as the patients involved in the studies from which the warning was generated. Furthermore, with caution about the higher doses of domperidone stemming from a study where so few patients were actually on higher doses, the Health Canada-endorsed warning regarding the use of domperidone in higher doses seems to be an over-reaction. Finally, taking into account the other drawbacks of these studies as outlined above, the evidence that domperidone actually causes ventricular arrhythmias or sudden cardiac death is not compelling' (126: p.3).

There is no record of this consensus statement being peer-reviewed or published in the medical literature and it includes no statement of conflict of interest by its authors or endorsers.

2.6.2 Efficacy and Safety of Domperidone

There is a lack of high-quality research evidence on the efficacy of domperidone in terms of whether it significantly increases a mother's breast milk supply. A systematic review of domperidone's efficacy and safety (unpublished) by Puil et al. (128) found that the quality of the randomized control trials (RCTs) that examined domperidone's efficacy was limited. Problems included small sample sizes, a primary focus on preterm rather than on full-term births, the inadequate measuring of outcomes such as the impact of domperidone on the duration of breastfeeding and a lack of comprehensive information on adverse drug reactions. There was no measurement of the efficacy of dose levels over 60 mg/day even though Canadian research (1) indicates these dose levels are frequently prescribed.

Among the RCTs that explored domperidone's effectiveness in increasing breast milk supply, four of the studies examined milk volume related to domperidone use versus placebo (129 – 132). These four studies looked only at preterm births and the participant levels within these studies were low (N = 109).

The lack of focus on domperidone use in mothers with preterm babies does not fully reflect domperidone use to treat LMS. In the BC research showing increasing rates of domperidone use, 86% of the mothers using domperidone to treat LMS gave birth to full-term infants (1).

Two RCTs (133, 134) involved preterm babies and compared different doses of domperidone rather than using a placebo comparator, two others compared domperidone against other medications (135, 136), one RTC involved mothers who had a caesarian section (137) and one looked at domperidone in conjunction with feeding schedule tolerance for post-caesarian section women (138).

Empower was a Canadian Institutes of Health Research (CIHR) funded RCT that compared domperidone with placebo and was designed to assess whether preterm babies were able to achieve an increase in breast milk supply if their mothers were given domperidone on or before 21 days post-delivery (139). Ninety (90) women were enrolled in the first phase of this study. The study intended to

enrol 560 participants but was terminated in 2015 because of a lack of enrollment. This was due to the study having to incorporate an enhanced consent process, required by Health Canada, that included providing more information to patients about the drug's cardiac risks. The study found that women using domperidone increased their milk supply but the volume of increase was modest and not statistically significant.

In another analysis, which considered the results of the four-placebo versus domperidone RCTs and the Empower Trial, Grzeskowiak et al. (140) concluded that, although domperidone may lead to a moderate short-term increase in milk supply, no data exists on whether this is sustained. The main outcome that was measured in these RCTs was milk volume as an indicator of the efficacy of domperidone. More meaningful outcomes, such as whether domperidone increased an infant's weight and/or had an impact on the exclusivity and duration of breastfeeding, were either not examined, or if addressed, involved minimal or short-term data collection.

The research literature has identified three potential safety concerns associated with domperidone use. The first relates to domperidone's function as a potent blocker of D2 receptors, not only in the gut but in the central nervous system, potentially leading to adverse effects associated with anti-psychotics such as risperidone (121, 141, 142). Although rare, neuroleptic malignant syndrome (NMS) can be a serious, sometimes fatal, complication of a neuroleptic medication, including domperidone. Spirt et al. (142) describe a case of NMS in a 47-year- old woman who had been taking Motilium (domperidone) orally at a dose of 30 mg three times a day. She experienced common symptoms of NMS including hyperthermia, muscle rigidity, hypertension, diaphoresis, tachycardia, elevated creatinine kinase and mental status changes such as confusion and agitation. The authors note that NMS can occur after a patient takes a single dose, after a dose adjustment or after the patient has been taking the drug for many years.

A second potential harm, described in the medical literature, is the potential for physiological and psychological symptoms which can occur when some patients withdraw from domperidone use. Two case reports describe these effects in women who were using domperidone to increase breast milk supply (143, 144). Both reports describe patients with unremarkable medical histories and no psychiatric disorders who were prescribed domperidone within the first week postpartum because they felt that their milk supply was inadequate. Both were on high doses of domperidone: 80 mg/day in one case and from 90 – 160 mg/day in the other. Both patients tapered their dose of domperidone over a 3 – 5-day period several months after their babies were born when they decided to stop breastfeeding. After an initial week of no symptoms post-taper, both experienced a variety of disturbing symptoms, including anxiety, agitation, panic attacks, and insomnia. These symptoms immediately disappeared when the previous dose of domperidone was reintroduced. Each recovered after undertaking a much slower taper of 8 – 12 weeks. Although the authors did not establish a clear cause for these withdrawal symptoms, they suggested that they were comparable to the symptoms experienced when

withdrawing from similar pharmacologic agents such as antipsychotics due to the upregulation of receptors.

The most serious adverse effect associated with domperidone is drug-induced prolongation of the QT interval of the heart (QT prolongation), a heart rhythm disorder. QT prolongation can be congenital, caused by electrolyte disorders or by QT-prolonging medications. Domperidone is a known QT-prolonging medication as are many other commonly used drugs including some antidepressants, antipsychotics, gastro-intestinal drugs, and antibiotics (145 – 147).

A long QT interval is a disorder of the heart's electrical activity. Heart beats are controlled by electrical signals which can be plotted on an ECG in five electric waves labelled P, Q, R, S, T. The length of electrical activity between the Q-T wave is called the QT interval and occurs in the lower or ventricular chambers of the heart. When the ventricles contract as part of this electrical activity (depolarisation), they must repolarize again in order to prepare for the next heartbeat. If some cells in the heart take too long to repolarize this results in a long QT interval. Repolarization and depolarization are affected by ion channels on the heart muscle which open and close to let sodium, calcium and potassium flow in and out of heart cells. In some cases, these channels can be blocked which contributes to QT prolongation. The QT interval is considered to be a biomarker for Sudden Cardiac Death (SCD) because with prolongation the cardiac repolarisation/depolarisation cycle can become more chaotic and the two separate events occur concurrently leading to ventricular dysrhythmias and Torsades de Pointes (TdP) which has a high rate of SCD (148 – 152). In summary, research has clearly established a relationship between the use of domperidone and its serious adverse effects including the potential for ventricular arrhythmias (VA), cardiac arrest or SCD (153 – 159).

Most of the studies on the cardiac risks of domperidone focus on the drug's approved uses as a prokinetic or antiemetic related to older populations. For example, Arana et al. (156) looked at the association of domperidone versus PPIs (proton pump inhibitors) and metoclopramide or non-users of these drugs in terms of out-of-hospital sudden cardiac death. The authors found a higher incidence of sudden cardiac death in the users of domperidone and this was higher in those aged 61 and over. The risk of SCD was dose-related.

Van Noord et al. (157) conducted a population-based, case-control study in 1996-97 using a primary care database in the Netherlands to assess the use of domperidone, daily dose and risk of serious non-fatal ventricular arrhythmia (VA) or SCD. The authors found a four-fold increase of SCD reported in domperidone users. The risk was dose-related with more than 30 mg/day presenting more risk. Only 12.7% of the participants were under 55 years of age.

Johannes et al. (158) examined the rate of SCD in users of domperidone compared to those using PPIs or non-users of these medications using electronic databases in Saskatchewan from

1990 – 2005. The authors found an increased risk of SVA/SCD among domperidone users. Again, this study was focused on older patients (mean age 79.4 years).

Between January 1, 1985 and August 15, 1986 Health Canada received nine case reports of heart and rhythm disorders, including TdP, related to domperidone among patients with a median age of 42. Most used domperidone for approved indications and the data did not establish causality (159).

A Summary Safety Review published in 2015 by Health Canada stated that cases supporting the association between domperidone and serious abnormal heart rhythms were reported worldwide. These included 342 reports of serious heart-related events in the manufacturer's database and 137 reports found in the World Health Organization (WHO) database (122).

Hill et al. (160) and Hill (161) estimated domperidone to be the cause of 231 cardiac deaths per year in the French population aged 18 years or over. The estimated exposure to domperidone was derived from national drug reimbursement claims, did not differentiate between on and off-label uses and included the reproductive age group. Domperidone is used off-label in France but these uses do not include using the drug to treat LMS.

The most focused examination of the relationship between domperidone used postpartum and VA was conducted by Smolina et al. in 2016 (162). This retrospective population-based cohort study looked at all women experiencing a live birth in BC between January 2002 and December 31, 2011 in order to estimate the rate of hospitalization for VA among women who were or were not exposed to domperidone. The exposure group had at least one prescription of domperidone for any indication. The study concluded that the risk of VA requiring hospitalization was rare. There were no hospitalizations for cardiac arrest and 21 hospitalizations for VA during the postpartum period. The risk of VA was approximately double among those exposed to domperidone, although this association was not statistically significant. This research study had limitations which affected the ability of the authors to fully assess the safety of domperidone. It lacked power due to the small number of identified outcomes and was unable to conduct dose-response analyses due to a lack of access to emergency room records.

Hondeghem and Logghe (163) recalculated data from a report by the European Medicines Agency on domperidone-associated cardiac events to determine the effects of age and sex. Using this and several other sources of data the authors calculated SCD among women aged 20 – 39 years who were treated for 2 – 4 weeks with domperidone. This reanalysis estimated that the probability was about 112 SCDs per million treatments of domperidone (at 30 mg/day). At higher doses, this would increase to 635 SCDs per million treatments. The authors consider that there is a higher propensity to proarrhythmias in women compared to men, by medications that block the hERG ion channels.

An additional safety concern is that domperidone is passed through breast milk without a clear understanding on how breastfeeding infants could be affected. Hondeghem (119) concluded that current studies are too limited to determine the safety of the drug for newborns. There is an added safety risk because the blood-brain barrier in infants is less mature than in adults, potentially making them more vulnerable to the effects of a drug like domperidone. Djeddi (164) found an association between QT prolongation and neonates who have been administered therapeutic doses of domperidone to treat gastroesophageal reflux.

2.6.3 Risk Factors for Drug-induced QT-prolongation

Both unmodifiable and modifiable risk factors can potentiate drug-induced QT prolongation such as what might occur with domperidone. Unmodifiable risk factors include female gender, increasing age, genetic predisposition, and structural heart disease. Potentially modifiable risk factors include the dose levels of the drug and the use of other QT-prolonging medicines that have the potential of affecting heart rhythms or causing electrolyte abnormalities (145).

Female gender is associated with a higher risk of QT prolongation because females have a slightly longer normal QT interval than males at baseline (149, 163, 165 – 167) and a faster heart rate. Vink et al. (166) describes gender-related differences in the QT interval which she indicates are likely the result of changes in sex specific hormones. The exact mechanisms behind the influence of sex hormones are not fully understood but after puberty testosterone appears to shorten the QT interval among males while that of females remains longer. Differences in QT intervals between males and females decreases with age so that gender ceases to be a contributor in women and men over 60. In females with an impaired repolarization process, the influence of sex hormones may be more pronounced, for example, early in the postpartum period.

Drici et al. (165) point out that two-thirds of the cases of TdP occur in women. Both the longer corrected QT interval (corrected for the heart rate) at baseline and a greater response to drugs that block potassium channels may facilitate the emergence of arrhythmia. The authors suggest that women are more likely to experience cardiac ADRs (adverse drug reactions) from non-cardiac drugs than men due to their different body composition and different metabolic processes that may affect the pharmacology of a drug. The authors concluded that:

> ‘Women are more prone to experiencing drug-induced adverse effects. Some of the reasons for this are the greater degree of polypharmacy, the increased bioavailability of drugs and a greater sensitivity of their target organs. Drug-induced LQTS with its associated torsades de pointes represents a particularly interesting model of female gender as a risk factor for adverse effects’ (p.582).

Increasing age is also seen as a non-modifiable risk factor for drug-induced QT prolongation by some researchers. Both Van Noord (157) and Johannes (158) described a higher incidence of QT prolongation among older adults. This may be due to the increasing prevalence of coronary heart

disease among older people. However, in their reanalysis of the European Medicines Agency's data on domperidone use and sudden cardiac death, Hondeghem and Logghe (163) found that domperidone use and SCD did not show a consistent association with age.

In terms of modifiable factors, taking more than one QT-prolonging drug is a significant risk factor for drug-induced QT prolongation. There is a large and growing list of medications that have QT-prolonging potential (145, 147). These include commonly used drugs such as antibiotics and anti-depressants. Ehrenpreis et al. (168), in a study of the electronic health records of all patients taking domperidone at a Washington Health Centre from January 1, 2008 to December 1, 2013 (N = 155), found that 69.7% of the research subjects were being prescribed other QT-interacting drugs along with domperidone. The authors concluded that:

> 'It has been our impression that despite known cardiac toxicity of domperidone, some practitioners do not follow the recommended practice of frequent electrocardiogram (ECG) monitoring in patients receiving the drug. In addition, there is limited prescribing information emphasizing interactions between domperidone and other QT-prolonging drugs. This situation is likely to place patients at risk for cardiac arrhythmias and sudden death resulting from these interactions and insufficient cardiac monitoring' (p.1).

Forbes et al. (169), in a study of the impact of the safety warnings of domperidone on prescribing at two tertiary care sites in Ontario, found that 59% of the study participants were being prescribed QT-prolonging drugs concurrently with domperidone before the Health Canada advisory of 2012 and 49% after the advisory, suggesting that concurrent prescribing of QT-prolonging drugs was and remains relatively common.

The cardiac risks of domperidone are also dose-related with doses of over 30 mg/day associated with higher risk of cardiac effects (157,158,163). The risks of dose levels over 30 mg/day are also reflected in safety advisories issued by the regulatory agencies such as European Medicines Agency (124) and Health Canada (170). However, findings from a study of breastfeeding mothers in BC (1) indicates a dramatic increase in the prescribing of domperidone postpartum and in daily dose levels. The proportion of patients receiving more than 80 mg/d increased from 11% in 2002 to 19% in 2011. By 2011, the majority of women being prescribed domperidone were receiving doses of over 30 mg per day and the proportion of this group was increasing over time. However, despite the increased risk of cardiac events with higher doses, only two RCTs carried out by Knoppert et al. (133) and Wan et al. (134) examined the effects of different dose levels of domperidone (30 mg and 60 mg/day) on milk volume. Neither study showed a significant increase in milk volume as a result of these two dose levels.

In summary, there is a lack of high quality RCT research on the efficacy of domperidone in terms of it producing significant increases to milk volume, even at higher dose levels. The research is characterized by small numbers of participants, limited outcome measurements, and short duration of testing and follow-up. Domperidone is also associated with risks which include neuroleptic malignant

syndrome, neuroleptic-like effects upon withdrawal from the drug and cardiac risks because of its QT-prolonging potential. Most of the research on domperidone's cardiac risks has focused on older women despite female gender and older age both being independent risk factors. A study in BC (162) among women of reproductive age found that there was an association between domperidone use and the risk of VA although this was not statistically significant. The study lacked power and did not have access to some medical records.

2.6.4 Health Warnings and Advisories Related to Domperidone

The intravenous formulation of domperidone was withdrawn from the global market in 1986. The drug is not currently approved in the US and is available only under the expanded access program (120). On June 7, 2004, the US Federal Drug Administration warned that distributing any domperidone-containing product, including to increase milk supply, is illegal because of the potential for serious health risks (171). However, domperidone can be purchased in the US through online pharmacies in Canada for any purpose, including off-label use. The degree to which domperidone is purchased online from the US and Canada from any source is unknown. One prominent Canadian breastfeeding support and information website provides information on how domperidone can be purchased through internet prescriptions in Canada (172). This information appears to be primarily directed to people living outside of Canada but there is no data available on those who are using this information.

One of the main policies and actions implemented by Health Canada to address the post-market safety of prescription drugs is through the dissemination of safety information about their potential risks to the public and health care providers. Health Canada uses a classification system (173) to designate these safety advisories as being of high, medium and low urgency depending on the severity of the drug risk being communicated. The classification system also determines how Health Canada communicates the risk message. Medium urgency risk communication is the most common type of risk communication issued by Health Canada. It relates to a Type II hazard where the use of a product may cause adverse health consequences or where the probability of serious adverse health consequences is remote. Medium urgency advisories also provide information about time sensitive issues regarding the safety and effectiveness of a product, where there is new safety information available about a product or in the case of a product withdrawal. Safety advisories are particularly important in cases where a drug is being prescribed off-label because clinical testing may be incomplete for unapproved uses.

Health Canada has issued two safety advisories of medium urgency related to domperidone. On March 2, 2012, a Dear Health Care Professional Letter was sent to many types of health care providers alerting them to the association of domperidone with serious ventricular arrhythmias and sudden cardiac death, particularly in patients taking daily doses greater than 30 mg and in those older

than 60 (174). Dear Health Care Professional Letters are targeted primarily to physicians. It is not clear whether midwives or lactation consultants are routinely included in this targeted communication.

A second Health Canada advisory, also of medium urgency, was issued to the general public on January 20, 2015 (127). It recommended that patients use domperidone at the lowest effective dose, for the shortest time possible and at a maximum dose of 30 milligrams per day. Health Canada Public Advisories are targeted towards consumers, patients, patient associations, the media and the general public. All advisories, no matter what group they are targeted to, are listed on the Health Canada MedEffect website and are distributed by email notification if a person registers for these notifications. Both Health Advisories on domperidone address approved uses of the drug and did not specifically address off-label uses. Risk communication policies are discussed in more detail in Chapter 5.0.

In 2014, the European Medicines Agency recommended that prescribing for domperidone be continued but restricted only to licensed uses, primarily the management of nausea and vomiting, at a recommended dose of no more than 30 milligrams daily for adults and for a recommended period of no more than one week (124).

In a review of the safety of drugs prescribed in France, the drug safety and efficacy journal Prescrire (175), identified domperidone as a drug to avoid because of its limited efficacy as a treatment for nausea, vomiting and gastro-esophageal reflux and its adverse effect profile. This recommendation was based on an analysis of the drug and its approved indications between 2000 – 2015. The UK Medicines and Healthcare products Regulatory Agency (MHRA) also issued a Dear Healthcare Professional Letter warning of the risk of cardiac affects associated with domperidone. The letter recommended that its use be restricted to treating nausea and vomiting and that the dose and duration of use be limited (176).

3.0 DESCRIPTION AND RESULTS OF ONLINE SURVEYS WITH CLINICIANS

3.1 Purpose of the Survey and Section Organization

The purpose of my research is to identify the key policy, prescriber, and patient factors that could help explain the rising rates of off-label prescribing of domperidone when it is used to treat LMS. In British Columbia, the rate of postpartum domperidone prescribing increased from 11 to 19% between 2002 and 2011 for mothers with full-term babies. Almost one in five mothers of full-term babies in BC in 2011 were using domperidone to increase their milk supply (1).

Separate online surveys with practicing and licensed midwives and with family physicians providing postpartum care in BC were developed in order to explore clinician practice and prescribing characteristics associated with the off-label prescribing of domperidone to treat LMS. The surveys included questions about clinician and practice characteristics, approaches clinicians use to treat LMS, the sources of information they use to establish domperidone's safety and efficacy, patient assessments carried out before prescribing, recommended dose levels and the outcomes of domperidone use for patients, including potential risks. Clinician awareness of Health Canada's advisories on domperidone and their perceptions of the relevance of these advisories to the off-label use of the drug to treat LMS were also examined in the survey.

The variables examined in the surveys correspond to key variables and concepts defined in the socio-ecological model described in Table 2 and as defined in the Conceptual Framework (Figure 1) which was the frame of reference for my research. The questions explored in the Physicians' and Midwives' Surveys address Level 1 of the SEM and the characteristics, beliefs, knowledge and practices of clinicians.

Section 3.2 of this chapter provides information on the planning, goals, process and content of the surveys that are comparable for both the midwives and physicians. Findings from the two surveys are presented in two separate sections, (Section 3.10 for the Midwives' Survey results and Section 3.11 for the Physicians' Survey). It was not the intention of this research to compare midwife and physician responses to the survey. Each professional group has a distinctive mandate and role. The results from each survey were analyzed and are reported separately.

3.2 Description of the Survey Respondents

BC Midwives are autonomous, primary care health professionals who provide maternity, newborn and six weeks of postpartum care. They work with other health professionals such as family physicians, obstetricians, nurses, pediatricians and lactation consultants both in hospital and in the community. My research included midwives because of their significant role in providing information, support and guidance about breastfeeding to parents before birth and during the first six weeks after birth, both in hospital and at home. BC licensed midwives attended approximately 20% of all births in

BC (177) and are trained to address breastfeeding problems, including LMS. Midwives also have had the authority to prescribe specific drugs related to their mandate, including domperidone, since 2009 (178). Prescribing guidelines for midwives, including those for domperidone, are included in the BC College of Nurses and Midwives formulary. As well as prescribing domperidone, midwives can recommend a medication to their patients with the suggestion that this be discussed with a family physician.

The research inclusion criteria for midwives participating in the online survey were that they be licensed by the College of Midwives of British Columbia, be actively practising in BC and have provided postpartum services to a minimum of two clients in the past six months. I included BC family physicians in a comparable online survey because previous research conducted in BC showed that most (92%) of the initial and subsequent prescriptions for domperidone written for mothers of full-term and preterm births in the postpartum period during the study period were written by general practitioners rather than specialists (1). The two inclusion criteria for physicians participating in the survey were that they were currently practising as a family physician in BC and had provided postpartum care to at least two patients within the past year. Family physicians provide most of the postpartum care to women in BC whether or not they provide prenatal or birthing services.

3.3 Reasons for Using an Online Survey Methodology

Online surveys are appropriate, low cost and efficient methodologies for understanding the experiences, opinions and behaviour of respondents when the recipient group is well defined, direct or indirect contact with the group is possible and where there is potential buy-in and support for the research question or purpose from the surveyed group. A disadvantage of online surveys is that they frequently have lower response rates than other methods such as telephone or face-to-face interviews and mail-out surveys. To address survey response concerns I incorporated Dillman et al.'s online survey techniques (179) related to survey construction, invitations and reminders. One of the key factors in increasing response rates is the use of multiple reminders sent to survey participants (179, 180). Both surveys included multiple reminders to potential respondents although these were targeted to the population rather than to specific individuals. The surveys included a consent letter and were designed to take only five minutes for participants to complete. Most questions were multiple choice.

3.4 Survey Questions and Variables

The Midwife and Family Physician Surveys included exactly the same questions with the exception of one question, which was added to the physicians' survey. Because most physicians do not receive specialized training on how to handle breastfeeding problems, this additional question asked how comfortable physicians felt treating these issues.

It was necessary to build each survey on a different survey platform. This was due to changes in the provision of survey software by the University of British Columbia which took place in early 2018. The Midwives Survey was built on a FluidSurveys software platform. FluidSurveys was originally a Canadian software company and was the recommended survey tool provided free to all UBC students at the time that the midwife survey was being planned and conducted. After it was sold to a US company it was no longer available to UBC students and by February 2018 had been replaced by Qualtrics software. The Physicians' Survey, which was conducted between April and August 2018, used the Qualtrics online survey platform.

In order to protect the data collected for the Midwife Survey which was deleted by FluidSurveys in February 2018 and use a congruent data entry and management system for both surveys, I used an interrelational database specifically designed to handle survey data (The Survey System) in order to manage and conduct my data analysis. The data was validated using internal validation tools and through three data entry processes and review of tables.

The survey questions collected data on the personal, practice and prescribing characteristics of clinicians which were then assessed in relation to their use of domperidone to treat LMS. To arrive at specific questions for the survey, I broke down the elements in my general and specific research questions related to clinicians. I also used findings from the literature, discussions with breastfeeding experts and members of my research committee to develop draft questions.

I used Eguale et al.'s study on off-label prescribing (2) to define key practice and personal questions for clinicians and to address issues like practice orientation through the types of knowledge clinicians relied on. Smolina et al.'s study (1) was used as a basis for a question on dose levels of domperidone. Patient testing questions were drawn from Health Canada's advisories and from the literature on the risks of domperidone and from health regulators. Questions on approaches used to address LMS were drawn from the literature and from discussions with breastfeeding experts.

Some research suggests that physicians are not always aware of off-label prescribing (22) so this was queried in the survey along with questions about clinician awareness about safety warnings. My research supervisor suggested other questions such as whether patients help drive prescriptions and whether physicians were comfortable handling breastfeeding issues. The questions were discussed with committee members multiple times before they were approved. Survey questions addressed the following question areas (Appendix I).

- Clinician personal and practice characteristics – gender identification, years in practice and the location of the clinician's practice.
- The number of patients with LMS that physicians had on their caseloads.
- The approaches that clinicians used to diagnose LMS – the use of six common evidence-based and qualitative approaches was assessed.

- Treatment approaches used by clinicians to address LMS – these included support, education, pharmacologic and non-pharmacologic galactagogues.
- The sources of information clinicians frequently used to determine domperidone's safety and efficacy – these included evidence-based and more anecdotal sources of information including Cochrane Systematic Reviews, Consensus Statements, and advice from colleagues.
- The type of clinical assessments clinicians recommended or used for their patients prior to prescribing domperidone. These assessments included taking a patient's cardiac history, inquiring about the use of other QT-prolonging drugs and ordering an ECG if risks were identified. In a guidance document on the use of domperidone, England's MHRA recommends ECGs prior to the initiation of treatment with domperidone and at one week after treatment has commenced in individuals who are taking over 30 mg/day and who may be at risk of developing QT prolongation (181).
- Clinician's view of the most effective dose of domperidone to treat LMS. Dose categories ranged from 30 mg/day to 80 mg/day and over.
- Clinician estimate of the effectiveness of domperidone in helping mothers exclusively breastfeed.
- The party (clinician or patient), who initiated discussions about using domperidone to treat LMS.
- Clinician awareness of whether prescribing domperidone for LMS is an on or off-label indication.
- Clinician knowledge of and response to Health Canada Health advisories on domperidone.
- Clinician assessment of the health and safety risks of domperidone for mothers and infants.
- Physicians' comfort treating breastfeeding problems (not asked of midwives).

The dependent variable originally identified in my research protocol and meant to be used in both the midwives' and physicians' surveys was whether or not clinicians prescribed domperidone to treat LMS. The unit of measurement was the clinician (midwife or family physician). Independent variables included all the clinician, practice, prescribing and treatment characteristics reflected in the survey questions described above (Appendix I).

The goal of my data analysis was to determine, through univariate, bivariate and a multiple logistic regression analyses, if any of the independent variables had statistically significant associations with the dependent variable. It was assumed that both surveys would have a mix of prescribers and non-prescribers of domperidone.

When the results from the surveys were analyzed, there was only one midwife who participated in the midwives' survey who did not prescribe domperidone. There was no evidence-based data that indicated this would be the case in advance of designing the research protocol.

Selection bias may have contributed to the lack of participation of midwives who did not prescribe domperidone to treat LMS (see Section 3.5).

An online survey of midwives on the management of deficient lactation in Switzerland and Canada (182) reported that 100% of the Canadian midwives said that they used domperidone to treat their clients. This survey involved a non-randomized convenience sample which provided limited details on the respondent group or the criteria used to select them. However, because only one midwife did not prescribe domperidone in my survey, this number was too low to constitute a non-prescribing group so this respondent was eliminated from the survey leaving only midwives who were using domperidone to treat LMS as survey participants.

The results from the midwives' survey made it impossible to use the dependent variable I had originally included in my research design – whether or not a clinician prescribed or did not prescribe domperidone to treat LMS. This necessitated the selection of a new dependent variable which needed to be drawn from the existing survey questions and had sufficient numbers to make up comparison groups. I chose the only question on the survey which indicated the degree to which clinicians prescribed domperidone to patients with LMS on their caseload. This survey question had four answer categories that included clinicians providing domperidone to 'most patients' (75% or more of their clients with LMS), 'many patients' (50 – 74% of their patients with LMS), 'some patients' (25 – 49% of their patients with LMS) and 'a few patients' (less than 25% of their patients with LMS).

I clustered the results of these four answer categories into two new categories which I used as a binary measure for my new dependent variable. The 'higher prescriber' category included all the clinicians who prescribed domperidone to 25% or more of their patients with LMS. The 'lowest prescriber' category included those clinicians who prescribed domperidone to less than 25% of their patients. This approach came closest to meeting the goal of identifying clinicians who were the least interested in using domperidone to treat LMS. I considered this to be the most reasonable approach, given the data that was available, to measure the concept I intended to measure (clinician interest in using domperidone as an approach to treating LMS) and thus could be considered to have face validity. I discussed this approach with another survey researcher, a statistician and my primary advisor who agreed it captured face validity.

It is recognized that there are limitations associated with using this measure. I was required to use pre-existing categories but was aware that my categorization of the lowest prescribers included some clinicians who were in the lowest end of the next category which included those prescribing to 25 – 49% of their clients. The label 'higher prescribing category' was meant to indicate a comparison to the 'lower prescribing' category and did not indicate that all the clinicians in this group were high prescribers. The data from this dependent variable was measured against all the independent personal, case, practice and prescribing variables that were reflected in the survey questions.

Although the Physicians' Survey also reported a relatively low number of physicians (14/161) who did not prescribe domperidone, I considered this group to be sufficient in size to be considered as a dependent variable. However, when questions on the physicians' survey only applied to those who were prescribing domperidone, I used the same dependent variable selected for the midwives' survey to analyze this set of questions.

3.5 Piloting the Surveys and Addressing Bias

The Physicians' Survey was piloted with two physicians and a lactation expert. The Midwife Survey was piloted with two lactation consultants and a physician who manages a breastfeeding clinic. Pilot reviewers were given guidelines for the review based on Dillman et al.'s (179) guidelines for appropriate formatting, organization, duration, question construction, comprehensiveness and validity. I, along with three other testers, checked the time duration of the survey multiple times online to see if it could be completed in five minutes or less. Feedback from the reviewers was incorporated into revised versions of the survey.

Social desirability bias relates to the tendency of respondents to sometimes provide socially acceptable responses that could present them in a positive light but which might not reflect their actual opinions. I considered that social desirability bias might influence the answers to several survey questions including the question on dose levels recommended by clinicians or on the information clinicians consulted in order to establish domperidone's effectiveness and safety when it is prescribed off-label.

There is limited evidence on the types of questions most likely to avoid social desirability bias. Some research suggests that the following aspects of survey development have the potential of limiting social desirability bias. The majority of these recommendations were incorporated into the development of the survey questions (183, 184). The recommendations included the following:

- the use of a self-administered survey method;
- assurances of confidentiality for respondents and clarification of the steps taken to achieve this (these were specified in the survey invitation/consent email);
- explicit assurances in the survey that the focus of the method is on respondent observations and experiences as noted in the tone of the consent letter and addressed in questions;
- question wording that was designed to be non-judgemental in tone;
- embedding more sensitive questions in a series of questions which were less sensitive;
- reviewing the potential for social desirability bias during the survey development and piloting phases.

Non-response bias occurs when there is a limited response to a research request. This was a concern in both the surveys. Lack of time to complete a survey and survey fatigue have been noted as problems with physician survey responses (185). Survey response rates are also higher when

there is direct contact with the survey participants rather than contact through a third party. Because of client privacy reasons, I did not have the capacity to contact clinicians directly but relied on third parties, (The Midwives Association of BC and selected Family Practice Divisions), to disseminate information about the survey through internal communication methods. It was left up to midwives and physicians to notice the survey invitation and determine whether they wanted to participate. These factors may have contributed to both non-response and selection bias. Selection bias might have contributed to the relatively low number of non-domperidone prescribers, particularly among the midwives, who responded to the survey. To minimize the potential for selection bias, the survey invitation described the research as exploring the different methods that clinicians use to treat LMS, including the use of domperidone. Other methods explored in the survey included clinicians providing information on improved breastfeeding techniques such as proper latch to the mother and recommending that the mother increase the frequency of breastfeeding or pumping.

3.6 Ethics Approval and Informed Consent

Ethics approval for this research was applied for and obtained through UBC's Clinical Research Ethics Board (UBC-HI7-01786). The research was approved on October 11, 2017 and this approval was updated in September 2020. Two amendments were previously sought and approved to broaden outreach for the recruitment of breastfeeding mothers for the qualitative interviews and the scope for midwife recruitment through contact with administrators at midwifery centres in the province.

The same informed consent procedures were used for both surveys. An informed consent letter attached to the survey link was distributed to physicians through internal communication methods by selected Family Practice Divisions and through weekly memos and its Facebook page by the Midwives Association of BC. The survey link was also sent to selected midwifery centres throughout BC.

When potential respondents clicked on the survey link, they received a consent letter that included information on the purpose, content and duration of the survey and who was distributing it. The consent letter also included information on the ways that respondent confidentiality would be protected, how the information would be used, the incentives offered and any risks participants could be exposed to by participating, as well as contact information for the Principal Investigator and UBC ethics personnel if respondents had concerns about the study. When a clinician clicked on the direct link to the survey after being shown the consent letter, this was considered to constitute implied consent to participate in the survey. The surveys did not collect identifying information about the survey respondents.

Anonymous online survey data from the Midwives Survey was downloaded from FluidSurveys and aggregated and analyzed using alpha-numeric coding in The Survey System, a data analysis software program for survey results. Data from the Physicians' Survey was stored on UBC's approved

survey data collection platform, Qualtrics, which is being securely maintained by UBC-IT. This data was downloaded onto The Survey System database with the Midwives' Survey results for data aggregation and analysis. It will be removed from Qualtrics after the research has been completed.

All the survey and other research data (anonymized transcripts from the mothers' interviews) are stored on a secured, password-protected single-use computer in the locked office of the student and will be available for five years after my PhD has been completed. At the end of this period, the need for the data will be reassessed based on the level of demands and, when deleted, will be double deleted from the computer. Hard copies of questionnaires and interviews will be shredded after the PhD is completed.

3.7 Use of Incentives to Encourage Survey Participation

Incentives for survey participants are recommended as one of the best ways to increase survey response rates (179, 185, 186). There is no consensus on the effectiveness of the size and types of incentives that are most useful for motivating respondents to complete a survey, however, an important motivating factor is the ease of retrieving the incentive. The incentive that was offered to physicians and midwives was the opportunity to enter into a draw for a $100.00 online Amazon.ca gift card. Draws were done randomly at the end of survey completion. Clinicians who wished to participate in the draw were required to enter their email contact information on a separate online survey that was not linked to the primary survey so answers could not be linked with the contact information. Five $100.00 gift cards were available for the physician draw and three for the midwives. These numbers were based on expected response rates.

3.8 Clinician Sampling and Recruitment

3.8.1 Sampling and Recruitment of Midwives

The information about the midwives' survey, survey invitation and link, which included the informed consent letter, were distributed to members of the Midwives Association of BC (MABC) via their internal communication postings. MABC is the professional association representing licensed and practising midwives and is registered under the *Societies Act*.

According to the College of Midwives of British Columbia's Annual Report (CMBC), in 2015 – 16 there were 247 registered midwives in BC as of March 31, 2016 (178). The CMBC regulates the practice of registered midwives and sets the standards for professional practice. This includes setting standards, limits and conditions for prescribing, ordering and administering therapeutics, including prescription drugs such as domperidone. However, membership in the Midwives Association of BC, which was my recruitment source is voluntary and may not represent all current practicing and licensed midwives.

It was not possible to verify how many licensed midwives were actively practising in BC and met the inclusion criteria for my research when it was conducted and might be likely to respond to the survey. My inclusion criteria were that midwives be members of MABC, that they be licensed in the province, be actively practising and have provided postpartum care to a minimum of two patients in the past six months.

My approach to the midwives' survey did not involve random sampling or the selection of a statistically significant sample. Instead, my outreach to members involved total population sampling of the members of the MABC. I considered that the response would constitute a convenience sample because it was dependent on whoever saw and responded to the survey invitation.

I also had no capacity to determine whether the respondents to the midwives' survey were representative of the population of midwives in BC as a whole because I lacked access to demographic or practice information from the MABC or the CMBC to compare my results to.

The first survey information, invitation to participate, consent form and online link to the survey was distributed by MABC to its members on December 18, 2017. Four reminders about the survey were sent by the Association to members between January 2 and February 15, 2018.

In order to maximize survey response rates, information about the survey was also sent to the office administrators of sixteen midwifery practice centres comprised of multiple midwives located in BC's Lower Mainland, Vancouver Island and the interior of the province. These centres were selected from an online search of centres that provide midwifery services in BC. No reminders were sent to these organizations.

3.8.2 Sampling and Recruitment of BC Family Physicians

The research inclusion criteria for family physicians were that they be currently practicing in BC as family physicians and have provided postpartum care to at least two patients within the past year. Family physicians were recruited by issuing survey invitations through a random sample of the 36 Family Practice Divisions (FPDs) in BC. Data from the BC College of Family Physicians indicated that there were 4582 family physicians in BC (187) and about 90% belonged to a FPD. Family physicians were recruited through randomly selected Family Practice Divisions (FPDs).

FPDs are the primary clinical practice and support organizations that represent family physicians throughout BC. The activities of physicians in the FPDs centre around the implementation of broader provincial health initiatives, supporting patient populations such as vulnerable seniors and those experiencing opioid addiction, and the carrying out of administrative tasks such as physician training and recruitment of physicians for the division. FPDs are funded by the General Practice Service Committee which is a partnership between the Government and the Doctors of BC. Doctors of BC is a voluntary association that represents physicians, residents and medical students in BC.

There are six geographical Family Practice Division Regions in the province that include thirty-six Family Practice Divisions. Each division can include a large city or a mix of small and larger towns. Data from the National Physicians Survey also indicated that 97% of family physicians in Canada provide direct patient care (188). I then estimated that there were approximately 4000 family physicians with membership in FPDs in BC that could potentially meet the inclusion criteria.

The 2007 National Physician Survey indicated that that 55.6% of family physicians in BC provided care to infants from one to 12 months of age, while 46.1% provide care to neonates <1 month (188). I averaged these figures to estimate that 51% of family physicians were providing postpartum care to the mother/baby dyad up to an infant's age of 12 months. Using the 51% figure and the baseline number for family physicians in BC of 4,000, I estimated that there were 2,040 family physicians in BC providing postpartum care and who would meet the study inclusion criteria.

A probability sample size calculation was undertaken to determine the minimum number of responses I would need to help ensure that the results from the physicians' survey could be considered representative of the population of family physicians in BC providing postpartum care. Using a random sample calculator, a confidence level of 90% and a margin of error of 5%. I determined that a sample size of 238 family physicians was needed. A further 15% was added to this sample size to take into account extra variability introduced by cluster sampling to reach a final minimum sample size of 274. This was the best sample size calculation I was able to determine given the available data in British Columbia.

Research on physicians' survey response rates suggests variable rates. Cunningham et al. (180) found survey response rates of specialists are in the range of 30 – 35%. However, contact with a BC family physician who coordinated research involving primary care physicians indicated response rates are often well under 20% (Dr. Patricia Gabriel, Personal Communication, January 4, 2018). For this reason, I estimated a response rate on the part of physicians who saw the invitation to the survey as being approximately 24%. However, research estimating response rates often reflects research where respondents are directly contacted about participating in research. My research was dependent on physicians reading and responding to a survey invitation included in general member communication sent out by the FPDs. There was no way of determining how many physicians read the research invitation.

In order to achieve a final sample size of 274, I estimated that 2,250 family physicians would need to be surveyed. Of this group, 51% or 1,147 were likely to provide postpartum care. A 24% response rate from this group would mean that 275 physicians could potentially complete the survey, thus meeting the sample size requirements.

I used a geographical one-stage cluster random sampling method based on two criteria to determine the inclusion of the FPDs in the study. The first was to identify urban population centres that had a population of 80,000 or more in 2016 as documented by Statistics Canada (189) and

determine whether these population centres were roughly contiguous with the population area covered by the FPDs. Sixteen (16) Family Practice Divisions, which represented four of the six geographic FPD regions, were identified using these population criteria. I then estimated the number of family physicians in each of these divisions using population figures drawn from the most recent Annual Reports posted on these sixteen FPD websites to determine whether they met my projected sample size needs.

The 16 FPDs that were selected were randomly sampled in three phases between March and May 2018 to determine their willingness to post the survey information. Two of the 16 FPDs declined to participate. The 14 FPDs that agreed to post the survey invitation were Chilliwack, Kelowna/Central Okanagan, Ridge Meadows, Nanaimo, North Shore, Vancouver, Southern Vancouver Island/Saanich, Victoria, Kamloops, Burnaby, Langley, Surrey/North Delta, Fraser Northwest and Abbotsford.

Each FPD required that I provide them with information about the purpose of my research, expectations for physician involvement, the incentives for participating, how confidentiality would be handled, whether commercial interests were involved and how the research subject was aligned with their goals prior to agreeing to post information about my research and the survey invitation link. Each of the FPDs used different methods of informing their members about research opportunities. These methods consisted of weekly or monthly postings or newsletters. The degree to which physicians looked at the information sent out by their FPDs could not be established. Some of the larger FPDs posted multiple research invitations for physicians.

The survey was accessible online to physicians and responses were collected between April and July 2018 and each set of physicians from the selected FPDs had between one to two months to respond, depending on when the FPD approved the research and sent invitations out. The active research phase involved maintaining contacts with FPDs to ensure the posting of the material and working with them to include reminders in subsequent FPD communication methods. Thirteen (13) of the FPDs agreed to post at least one reminder about the survey to their members but it was not possible in some of the divisions to determine whether this took place.

3.9 Analyzing Survey Results

There were two dependent variables considered in the analysis of the physician survey results. The first dependent variable was whether or not a physician prescribed domperidone to treat LMS. This was analyzed in relation to independent variables addressed in the survey questions including physician demographic and practice characteristics, approaches to assessing LMS and methods used to treat it, knowledge of domperidone's off-label use (OLU) status, awareness and applicability of Health Canada advisories and assessments of risks to patients and infants.

The second dependent variable was applied only to those physicians who prescribed domperidone to treat LMS. This variable measured the estimated percentage of patients on the

physician's caseload who had LMS and were prescribed domperidone. It was used as a surrogate measure for clinician interest in and commitment to using domperidone to treat this condition. Using this variable, 78.8% (115/146) of the physicians were in the higher prescribing category and were considered to have a higher level of commitment to using domperidone as a treatment for LMS and 21.2% (31/146) were in the lower prescribing category (NR or no response = 1]) which I considered to represent a lesser degree of commitment to a pharmacologic approach for treating LMS.

This dependent variable was measured in association with independent variables most closely linked to prescribing, such as the information sources the physician used to establish domperidone's safety and efficacy, dose levels recommended, and the specific patient testing physicians used prior to prescribing the drug. All the data from the midwives' survey was analyzed using this dependent variable.

The data analysis process for both the midwives' and physicians' results included the following steps:

- The development of a code book to ensure the inclusion of all table labels and variables included in the survey questions in the data entry process and table generation, to enable the checking of data, to identify and add missing data and to reduce errors in the data entry and analysis process.
- The downloading of data from the survey platforms (FluidSurvey for the Midwives Survey and Qualtrics for the Physicians Survey) and re-entering the data into The Survey System in order to have a consistent analytical tool for both sets of data.
- The cleaning, filtering and validating of the data entered in The Survey System. Validation tools on The Survey System were used to identify basic errors in data entry. A duplicate data entry process and the generation and review of tables identified missing data and data entry errors. The data was cleaned and data analysis filters and a range of analytical methods were incorporated into the data analysis allowing the comparison of cross variables and the generation of descriptive statistics as well as the analysis of some tables by chi-square.
- The completion of the univariate analysis which involved analyzing and reporting the data using descriptive statistics (frequency tables). Multiple row data was clustered for some of the frequency tables.
- The completion of a bivariate analysis using chi-square to assess the associations between the dependent and independent variables. The confidence level was set at $p < 0.05$. Where data cells included 0 or there were more than 20% of the cells with fewer than 5 cases, a Fisher's Exact (FE) Test was used. An online calculator was used to conduct the Fisher's Exact Test which was not available in The Survey System. The results of the FE tests were validated by a statistician through a duplicate analysis using R.

- Conducting a post-hoc pairwise analysis among the multiple levels of given independent variables in cases where the bivariate analysis indicated there was a significant association between the dependent and independent variables ($p < 0.05$). Further 2 X 2 Fisher's Exact Tests identified what specific levels of the independent variable in the test were most related to the dependent binary variables.
- The construction of a multiple fitted logistic regression analysis was undertaken to measure the effects of each independent variable on the dependent variables for the results that showed significance in the bivariate analysis.

The results of the data analysis are reported separately for the Midwives' and Physicians' Surveys in Sections 3.10 and 3.11.

3.10 Findings from the Midwives' Survey

3.10.1 Background to the Midwives' Survey Findings

This section presents the findings from the analysis of data from the survey of BC licensed and practicing midwives. Results from the bivariate, pairwise and logistic regression analyses are included. The bivariate analysis used the chi-square or Fisher's Exact Test with a significance level of $p < 0.05$. This section also includes an analysis of the qualitative comments of midwives made about aspects of using domperidone and treating LMS. A summary of the key findings from the Midwives' Survey is in Section 3.10.17.

3.10.2 Midwives' Participation Level

Seventy (70) midwives opened the survey link. Nine respondents (12.9%) opened the survey link but did not proceed to answer any questions and two respondents (2.9%) answered fewer than three of the survey questions; both groups were not included in the survey analysis. In total, 59 midwives opted to participate in the survey. One midwife did not prescribe domperidone so was also removed from the analysis. This left a baseline group for the analysis of 58 midwives, all of whom prescribed domperidone to their clients.

3.10.3 Midwives' Personal and Practice Characteristics

The majority of the midwives, 89.7% (52/58), self-identified as female: 10.3% (6/58) did not identify their gender. The majority of the midwives (73.2% or 41/56) had been practising less than ten years; 17.9% (10/56) had been in practice for 10 – 19 years, and a small percentage (8.9% or 5/56) had practiced for 20 years or more.

Forty percent (40%) of the midwives who participated in the survey were practicing in the Vancouver/Lower Mainland and 60% had practices in the rest of the province. The chi-square analysis indicated that there was a significant association between the location of the midwives'

practice and how frequently they prescribed domperidone to their patients with LMS. The reasons for this association were not explored in the research (see Table 4).

Table 4: Midwives' Practice Location

Location	Total*	Higher Prescribers	Lowest Prescribers
	50	32	18
Vancouver/Lower Mainland	20 40.0%	17 53.1% 85.0%	3 16.7% 15.0%
Outside Vancouver	30 60.0%	15 46.9% 50.0%	15 83.3% 50.0%

Fisher's Exact Test: $p = 0.0163$
*NR = 8

3.10.4 Prevalence of LMS on Midwives' Caseloads

Survey results indicated that three-quarters of the midwives had ten or fewer clients with LMS in the past year. I was unable to estimate the percentage of patients on caseloads who had LMS because of a lack of information on the size of each midwife's caseload. A Fisher's Exact test found a significant association between the number of clients treated with LMS on the caseload and the percentage of clients who were prescribed domperidone (see Table 5).

Table 5: Midwives' Caseload Size and Frequency of Domperidone Prescribing

Number of Clients with LMS on Caseload	Total	Higher Prescribers	Lowest Prescribers
	58	38	20
Over 20	6 10.3%	6 15.8% 100.0%	0 0.0% 0.0%
11-20	6 10.3%	4 10.5% 66.7%	2 33.3%
6-10	30 51.7%	22 57.9% 73.3%	8 40.0% 26.7%
1-5	15 25.9%	6 15.8% 40.0%	9 45.0% 60.0%
None	1 1.7%	0 0.0% 0.0%	1 5.0% 100.0%

Fisher's Exact Test: $p = 0.0260$

3.10.5 Approaches Midwives Used to Diagnose LMS

Midwives were asked to describe how frequently they used six commonly used methods to assess whether their clients had LMS. Frequency of use was measured at three levels. The methods ranged from being highly qualitative (mothers' reports of baby behavioural cues), evidence-based (test/retest baby weighing) or those supported by clinical practice (checking for signs of dehydration through a daily count of wet diapers).

The two most frequently used methods, identified by 90% of the midwives, were the mother's recounting of baby cues/behaviours such as fussiness that they considered could indicate low milk supply and a daily count of wet diapers. The approach that midwives said that they used least frequently was the test/retest weighing of the infant after feedings (see Table 6). One association between an assessment method and the dependent variable (level of prescribing of domperidone to clients with LMS) was found. This was the clinician's use of the mother's reports of low milk supply as a way of diagnosing LMS (see Table 7). All approaches are reported in Table 6.

Table 6: Approaches Midwives Used to Diagnose LMS

Methods	Total	Use Frequently/ Most of the Time	Use Half the Time/Once in a While	Never Use	*p*-values
Test/test of baby weight	56 100%	13 23.2%	29 51.8%	14 25.0%	0.259
Mother's assessment of baby cues	58 100%	54 93.1%	4 6.9%	0 0.0%	1.000
Measurement of breastmilk volume	58 100%	18 31.0%	32 55.2%	8 13.8%	0.186
Mothers' reports of low milk supply	58 100%	34 58.6%	20 34.5%	4 6.9%	0.0204
Number wet diapers/day	58 100%	53 91.4%	4 6.9%	1 1.7%	0.1780
Tracking of baby weight on growth curve	58 100%	43 74.1%	11 19%	4 6.9%	0.2134

Table 7: Midwives' Diagnosis of LMS Using Mothers' Reports

Mothers' Reports	Total*	Higher Prescribers	Lowest Prescribers
	58	38	20
Frequently/Most of the time	34 58.6%	23 60.5% 67.7%	11 55.0% 32.3%
Half or some of the time	20 34.5%	15 39.5% 75.0%	5 25.0% 25.0%
Never use the method	4 6.9%	0 0.0% 0.0%	4 20.0% 100.0%

Fisher's Exact Test: $p = 0.0204$

3.10.6 Approaches Midwives Used to Treat LMS

The survey asked midwives to identify all of the approaches they used to treat LMS from a dropdown list of eight different approaches that are commonly used. Approaches included pharmacologic and non-pharmacologic methods.

Four approaches were used by all the midwives. There was no statistical association between the other approaches and the dependent variable.

Table 8: Approaches Midwives Used to Treat LMS

Treatment Approaches	Total	Used Approach	Did not Use Approach	*p*-values
Increase frequency of breastfeeding or pumping	58 100%	58 100%	0 0.0%	n/a
Reduce supplementation	58 100%	21 36.2%	37 63.8%	0.312
Provide information on lactation techniques	58 100%	58 100.0%	0 0.0%	n/a
Provide information/ reassurance about lactation	58 100%	56 96.6%	2 3.4%	0.115
Discuss impact of birth/personal experiences on breastfeeding	58 100%	44 75.9%	14 24.1%	0.449
Recommend non-prescription galactogogues	58 100%	58 100.0%	0 0.0%	n/a

Treatment Approaches	Total	Used Approach	Did not Use Approach	*p*-values
Refer patient to lactation consultant/ expert	58 100%	58 100.0%	0 0.0%	n/a
Prescribe or recommend domperidone	58 100%	58 100.0%	0 0.0%	n/a

3.10.7 Information Sources Midwives Consider Most Useful

Midwives were asked to identify all of the sources of information that they found most useful for assessing the safety and effectiveness of domperidone when used to treat LMS (see Table 9). A check-list of thirteen common sources of information on prescription drugs was provided. These included evidence-based sources such as Cochrane or other independent systematic reviews and research published in the medical literature and information that has a lower level of evidence such as consensus statements by experts, the midwife's own clinical experience and feedback from patients.

There was no information source that was universally considered as most useful by all of the midwives. However, consensus statements were the most frequently noted useful source of information about domperidone and were named by 80% of the midwives. The only existing consensus statement on domperidone to treat LMS is the "Consensus Statement on the Use of Domperidone to Support Lactation" (126). This document was written in 2012 and is co-authored by a number of lactation researchers including Dr. Jack Newman.

Dr. Newman is a physician in Toronto who has provided breastfeeding information and support to breastfeeding mothers for many years through his book, advocacy and website, currently the Canadian Breastfeeding Foundation (172). The consensus statement describes domperidone, when used as a galactogogue among reproductive age women, as posing minimal safety risks. Dr Newman has also advocated doses of domperidone much higher than the guidelines recommended by Health Canada and the European Medicines agency for some women.

Information from Professional Associations and Colleges was also rated as a "most useful" information resource by over 80% of the midwives. The College of Midwives of British Columbia is the governing body for BC midwives. It enforces standards, regulations and the practices of BC midwives and provides guidelines on prescribing drugs such as domperidone.

Midwives' personal clinical experience with domperidone as a treatment for LMS was considered to be the third most useful resource by 70% of the midwives. Cochrane and other independent systematic reviews were considered by 67% of the midwives to be a useful resource (see Table 9).

A measurement of the association between whether the midwives found these information resources on domperidone useful for establishing the drug's safety and effectiveness in relation to the dependent variable (level of prescribing of domperidone to clients with LMS) found no statistically significant associations. The *p*-values from these bivariate analyses are included in Table 9.

Table 9: Information Sources Midwives Consider Most Useful

Information Source	Total	Information Source Considered Useful	Information Source Not Considered Useful	Ranking	*p*-values
Consensus Statements	58 100%	47 81.0%	11 19.0%	1	0.395
Professional Associations	58 100%	47 81.0%	11 19.0%	1	0.731
Personal Experience with the Drug	58 100%	41 70.7%	17 29.3%	2	0.933
Health Canada Reviews/Advisories	58 100%	39 67.2%	19 32.8%	3	0.50
Cochrane and Independent Systematic Reviews	58 100%	39 67.2%	19 32.8%	4	0.394
Advice from Colleagues	58 100%	37 63.8%	21 36.2%	5	0.663
Patient Feedback	58 100%	33 56.9%	25 43.1%	6	0.832
Online/Internet Sources	58 100%	32 55.2%	26 44.8%	7	0.592
Research in Medical Literature	58 100%	25 43.1%	33 56.9%	8	0.729
Textbooks on Breastfeeding	58 100%	23 39.7%	35 60.3%	9	0.969
Workshops/Seminars/ Lectures	58 100%	22 37.9%	36 62.1%	9	0.814
CPS (Compendium of Pharmaceutical Specialities)	58 100%	8 13.8%	50 86.2%	10	0.701
Information from Drug Manufacturers	58 100%	6 10.3%	52 89.7%	11	0.635

Ten percent (10%) of the midwives (6/58) identified resources that they found useful in assessing domperidone's effectiveness and safety in an open-ended question. Four midwives identified Dr. Jack Newman's website and literature, one recommended the College of Midwives of BC and the other said "specialities" which was not defined further.

3.10.8 Patient Assessments Conducted by Midwives

QT-prolonging drugs, like domperidone, pose cardiac risks. For this reason, the research literature, Product Monograph and Health Canada warnings (116, 168, 171) have stressed the importance of healthcare providers assessing potential patient risks prior to prescribing the drug.

The first assessment involved the clinician taking a standard patient and family cardiac history and assessing whether the patient had health problems that might affect electrolyte balance such as eating disorders. The second assessment involved the clinician identifying any other QT-prolonging medications that the patient was taking. The use of concomitant QT-prolonging drugs increases cardiac risk. The third type of patient assessment was whether and how frequently a clinician ordered an ECG in order to further assess patients considered to have an increased risk.

Taking a client's cardiac history and reviewing whether the client was taking other QT-prolonging drugs were carried out always or frequently by over 85% of the midwives who completed the survey. However, ECGs were rarely ordered or recommended (see Table 10). There was no statistical association between whether or not midwives ordered any of these tests and the dependent variable that measured the degree to which midwives prescribed domperidone to their clients with LMS. These results are reported in Table 10.

Table 10: Patient Assessments Conducted by Midwives

Assessments	Total	Always/Most of the Time	About Half the Time	Once in a While/Never	*p*-values
Taking patient/family cardiac history	58 100%	56 96.5%	0 0.0%	2 3.5%	1.000
Assessing patient use of other QT-prolonging drugs	58 100%	50 86.2%	0 0.0%	8 13.8%	0.1096
ECG	58 100%	4 6.9%	1 1.7%	53 91.4%	0.7423

There was no statistical association between the frequency with which these tests were recommended or ordered by midwives and the dependent variable.

3.10.9 Dose Levels of Domperidone Recommended by Midwives

Eighty-one percent (81%) (47/58) of the midwives provided specific data on the dose level of domperidone that they believed was most effective to treat LMS. This question avoided asking midwives for the exact dose they prescribed or recommended in order to avoid sensitivity bias. Sensitivity bias can occur when a respondent answers a question in a way that does not represent their actual views because of external or other influences. Eleven (11) of the midwives indicated a

range of doses that could not be classified within the dose levels specified in the question, for example those who said that the dose depended on the needs of the patient or varied between 30 to 60 mg/day.

Less than a third of the midwives (27.7% or 13/47) who identified a specific dose level considered 30 mg/day to be the most effective. This is the dose level that Health Canada (171) and the EMA (124) have recommended as the safest dose for domperidone, however, these advisories did not specifically mention doses specific for the treatment of LMS because this use is off-label. Almost 60% of the midwives (27/47) recommended dose levels of 80 milligrams/day or more.

An analysis of the association between the dependent variable and the doses recommended by midwives that were above or at the recommended guideline of 30 mg/day was undertaken. This association was not statistically significant (see Table 11).

Table 11: Domperidone Dose Levels Recommended by Midwives

Dose Level	Total	Higher Prescribers	Lowest Prescribers
	47	31	16
30 mg/day	13 27.7%	7 22.6% 53.8%	6 37.5% 46.2%
Above 30 mg/day	34 72.3%	24 77.4% 70.6%	10 62.5% 29.4%

Chi-square: $p = 0.2786$

3.10.10 Midwives' Estimate of Domperidone's Impact on Breastfeeding

The survey asked midwives to estimate the degree to which they believed that the use of domperidone helped their clients' breastfeeding without supplementation or donor milk. Exclusive breastfeeding is a common goal of mothers when they begin to breastfeed.

Only one midwife said that none of her clients achieved this objective so this category was clustered with "a few" in Table 12. The results of this table indicated that just over half of the midwives believed that domperidone helped many mothers (over 50%) to exclusively breastfeed. There was no association between the midwives' perception of domperidone's effectiveness in enabling exclusive breastfeeding and the rate of domperidone prescribing on the caseloads of midwives (see Table 12). How midwives estimated the effectiveness of domperidone and to what degree exclusive breastfeeding continued while the mother was using domperidone were not explored in the survey.

Table 12: Midwives' Estimate of Domperidone's Impact on Exclusive Breastfeeding*

Midwives' Estimate of Percentage of Patients Able to Exclusively Breastfeed After Domperidone	Total*	Higher Prescribers	Lowest Prescribers
	51	34	17
Almost all (over 75%)	7 13.7%	4 11.8% 57.1%	3 17.6% 42.9%
Many (50-74%)	23 45.1%	14 41.2% 60.9%	9 52.9% 39.1%
Some (25-49%)	15 29.4%	12 35.3% 80.0%	3 17.6% 20.0%
A few (under 25%) or none	6 11.8%	4 11.8% 66.7%	2 11.8% 33.3%

Fisher's Exact Test: $p = 0.5806$
* Not reported: Seven (7) midwives said that they were uncertain about domperidone's impact.

3.10.11 Midwives' Estimate of Who Initiated Discussions on Domperidone

Midwives were asked to estimate the percentage of clients with LMS on their caseloads who initiated discussions about using domperidone prior to their midwife mentioning it. This question was asked to see if patients sometimes helped drive prescribing decisions. Although just over 10% of the midwives said that this never happened, over a third said that 25% or more of their clients mentioned domperidone as a treatment option first. There was no association between who initiated the discussion first and the level of domperidone prescribing by midwives (see Table 13).

Table 13: Midwives' Estimate of Who Initiated Discussions of Domperidone

Percentage of Clients	Total*	Higher Prescribers	Lowest Prescribers
	56	37	19
Over half of clients	8 14.3%	6 16.2% 75.0%	2 10.5% 25.0%
Between 25% -50%	12 21.4%	9 24.3% 75.0%	3 15.8% 25.0%
Less than 25%	30 53.6%	17 46.0% 56.7%	13 68.4% 43.3%
Never happens	6 10.7%	5 13.5% 83.3%	1 5.3% 16.7%

Fisher's Exact Test: $p = 0.5033$
*NR = 2

3.10.12 Midwives' Knowledge of Domperidone's Off-label Status

The use of domperidone to treat LMS is not approved by Health Canada. The survey examined the degree to which midwives were aware that using domperidone to increase breast milk supply is an off-label or unapproved use. Over ninety percent (92.7% or 51/55) of the midwives were aware that using domperidone to treat LMS is an off-label use; 7.3% (4/55) were not aware. There was no association between the midwives' knowledge of domperidone's off-label status and the dependent variable ($p = 1.000$)

3.10.13 Midwives' Awareness of and Response to Health Canada's Advisories

Health Canada issued two safety advisories about domperidone to the public and healthcare professionals in 2012 and 2015. The advisories did not specifically reference the off-label use of domperidone to treat LMS but focused on its approved uses as a prokinetic or antiemetic. The advisories discussed the cardiac risks of domperidone as a QT-prolonging drug. They recommended maximum dose levels of 30 mg/day as well as the use of drug for a short duration and discussed aspects of risk assessment such as reviewing the patient's use of other QT-prolonging drugs.

Midwives were asked if they were aware of one or more of these advisories. Since the advisories did not mention domperidone as a treatment for LMS, a related question asked midwives whether they thought the advisories were applicable to this off-label use.

All of the midwives who answered the question said that they were aware of the Health Canada safety advisories on domperidone (NR = 2). When asked whether they thought the Health Canada Advisories were applicable to domperidone's use as a galactogogue, 70% felt that the

advisories had limited or no applicability (see Table 14). Only 14% felt that they were fully applicable. There was no association between midwives' views of the applicability of Health Canada's health advisories on domperidone and the dependent variable.

Table 14: Midwives' View of the Applicability of Domperidone Advisories*

Applicability of Advisories	Total*	Higher Prescribers	Lowest Prescribers
	56	37	19
Fully applicable	8 14.3%	7 18.9% 87.5%	1 5.3% 12.5%
Quite applicable	9 16.1%	5 13.5% 55.6%	4 21.0% 44.4%
Somewhat applicable	34 60.7%	22 59.5% 64.7%	12 63.2% 35.3%
Not applicable	5 8.9%	3 8.1% 60.0%	2 10.5% 40.0%

Fisher's Exact Test: $p = 0.5597$
*NR = 2

3.10.14 Midwives' Assessment of Domperidone's Risks to Mothers and Babies

Over 80% of the midwives believed domperidone posed no significant or minimal risks to mothers treated for LMS. There was no association between the midwives' assessment of patient risks and their level of prescribing of domperidone to patients on their caseloads (see Table 15).

Table 15: Midwives' Assessment of Domperidone's Risks to Mothers

Risk to Patients	Total*	Higher Prescribers	Lowest Prescribers
Base	55	37	18
No significant risks	4 7.3%	4 10.8% 100.0%	0 0.0% 0.0%
Minimal risks	42 76.4%	26 70.3% 61.9%	16 88.9% 38.1%
Moderate risks	8 14.5%	6 16.2% 75.0%	2 11.1% 25.0%
Significant risks	1 1.8%	1 2.7% 100.0%	0 0.0% 0.0%

Fisher's Exact Test: $p = 0.4814$
*NR = 2, Uncertain = 1

All of the midwives who answered the question said that domperidone posed no significant or minimal risks to infants. There was no association between the assessment of risks to infants and the dependent variable (see Table 16). However, nine midwives (not included in the table), expressed uncertainty about the drug's risk to infants.

Table 16: Midwives' Assessment of Domperidone's Risk to Infants*

Risk to Infants	Total*	Higher Prescribers	Lower Prescribers
	47	33	14
No significant risks	28 59.6%	19 57.6% 67.9%	9 64.3% 32.1%
Minimal risks	19 40.4%	14 42.4% 73.7%	5 35.7% 26.3%
Moderate risks	0 0.0%	0 0.0% 0.0%	0 0.0% 0.0%
Significant risks	0 0.0% 0.0%	0 0.0% 0.0%	0 0.0% 0.0%

Fishers Exact Test: $p = 0.7532$
*Uncertain = 9, NR = 2

3.10.15 Midwives' Experiences with Domperidone

An open-ended question asked midwives to comment on their general experiences using domperidone to treat LMS. Another open-ended question on the survey which asked for comments on dose levels also generated some general comments on domperidone use. Both sets of comments were amalgamated and analysed together within one thematic analysis. Almost 30% (17/58) of the midwives made comments and some made more than one.

A four-stage thematic coding method was used to analyze comments from the midwives, to define theme labels and to categorize the results into themes. Comments were initially coded into comparable clusters by general comment. Initial broad coding labels were developed using the clustered theme areas. Comments were then moved or recoded using these pre-defined labels in order to establish internal consistency within the coding categories. A final blind coding was done using the coding labels to ensure consistency. The final coding labels were: domperidone dose, research, effectiveness, breastfeeding goals of patients, safety and use.

The number of comments per category were related to domperidone effectiveness (N = 10), dose (N = 7), safety (N = 6), use (N = 4), research (N = 3) and breastfeeding goals (N = 1).

Five out of ten midwives who had comments related to domperidone's effectiveness said that doses over 30 mg/day were the most effective for treating LMS. They were concerned that the new guidelines would mean they would be less able to help their clients with milk supply problems:

> "I was very saddened to learn that midwife regulations in BC recently decreased the prescribing dose of domperidone to 10 mg TID and for a limited length of time. These new regulations are not likely to aid many breastfeeding women. I hope this may someday change."

Three respondents said that using domperidone should be the last option after other approaches had been considered, including providing the mother with intensive support, education and encouragement. One of these midwives described the multiple factors that could lead to a woman feeling she had low milk supply, some of which were triggered by the types of care new mothers were given in hospital:

> "I feel like the use of domperidone is a bit of a Band-Aid solution to a larger problem. I feel that "low milk supply" is often diagnosed when, in fact, under different circumstances, milk supply may have been fine. Even though I work in a hospital with a 'baby-friendly' designation, I still find that babies are often needlessly supplemented in the first few days when they are in hospital. For many women, their confidence is undermined by different messaging among health care providers. Babies are often weighed too frequently and supplemented too often when more education and patience may have been all that was needed. Many women want quick fixes or feel the need to 'catch up' from a bad start. I have seen domperidone work really well and very quickly for some women, but I feel that it is sometimes offered too quickly. I have also seen it make little to no difference in some cases . . . . I see domperidone as one of the many tools I can opt to use, but it is by no means the first thing I jump to, nor do I believe it to be completely without risk."

Seven midwives made comments on the appropriate dose levels of domperidone when being used to treat LMS. These views were mixed. Four midwives stated that high doses were the most effective for treating LMS. One midwife said that the current dose guidelines should be maintained and two said that dose levels needed to reflect the needs of individual mothers so were variable.

Six respondents made comments about the safety of domperidone. One midwife said that she felt the risks of using domperidone were minimal for the majority of, but not all, mothers:

> "I feel that most healthy women of childbearing and breastfeeding age are at minimal risk when using domperidone. However, some women will be at significant risk if they have heart problems – known and unknown."

Two midwives expressed caution about using the drug because of its potential risks and two said that in some cases they would refer a mother to a physician for follow-up if a mother wanted to take a higher dose.

> "I rarely prescribe domperidone unless clients bring it up themselves either from their own research or previous use – in that case I review the new evidence and recommendations with them, screen for concerning health conditions/medications that would be contraindicated and do not feel comfortable using this medication. For women who desire a higher dose I have them see their GPs for more long-term follow-up."

One midwife said that she had used domperidone fairly regularly to treat LMS and that no mother had reported experiencing an ADR from using the drug.

The need for more research on domperidone as a treatment for LMS was highlighted by three midwives. One noted that most of the research on domperidone seemed concentrated on older women rather than women in the reproductive age group. Another wanted to have more research information on the use of domperidone to treat LMS in general. A third said that she was unaware of any research on the safety of domperidone for infants who were receiving it through breastmilk so wanted information on this topic.

Under the theme of goals of treatment one midwife noted that the goal of using domperidone was not necessarily to achieve exclusive breastfeeding. She said that:

> "Your (survey) question about what percentage have full milk supply on domperidone implies that this is the goal for using it - it often isn't. Mostly it's to give the mom the best chance to make as much milk as she can and give her baby as much of her milk as possible."

Five midwives commented on other aspects of using domperidone. One midwife said that an ECG to test mothers for potential cardiac problems prior to prescribing was not within the scope of midwifery practice. (The survey asked whether midwives had recommended or ordered the test.) Another midwife said domperidone should be initiated early and a second comment was that it needed to be tapered off slowly. Two midwives expressed concerns that domperidone was often prescribed too early in the postpartum period.

These general comments about domperidone by midwives were varied and touched a number of subjects. However, one theme was dominant. A third of the midwives who made comments expressed concern about new guidelines from the College of Midwives of British Columbia recommending daily doses of domperidone of 30 mg/day. These midwives believed that higher doses are often required in order to treat LMS effectively and that these new guidelines had restricted their treatment options.

3.10.16 Further Findings from the Midwives' Survey

This section presents the results of a further analysis of the Midwives' Survey data including findings from a post-hoc pairwise analysis among the multiple levels of the given independent variables when the bivariate analysis indicated an association between the dependent and independent variables. This section also includes the results of the multiple logistic regression analysis.

The dependent variable used to analyze the midwives' survey data was the frequency at which midwives prescribed domperidone to clients on their caseload with LMS.

The post-hoc pairwise analysis applied to tables with more than two levels, using an adjusted Fisher's Exact Test with a confidence level of $p < 0.1$. The results of the post-hoc pairwise analysis of one table indicated the following:

- **Table 7: Midwives' Diagnosis of LMS Using Mothers Reports and Frequency of Domperidone Prescribing.** The three levels in the question using mothers' reports to determine LMS by healthcare providers indicated the following patterns – reports of having LMS 1) frequently/most of the time; 2) half/some of the time; and 3) never used were related to the frequency of domperidone prescribing by midwives on their caseloads, using an adjusted $p = 0.0555$ and 0.0357 respectively using a significance level of < 0.1.

A multiple logistic regression analysis was used to determine whether the dependent variable (higher and lower prescribers of domperidone to clients with LMS) was associated with the

independent variables in the three tables where there was a significant association as determined in the bivariate analysis.

The midwives' raw dataset consisted of 58 midwives which was reduced to 50 after missing cases among the dependent and independent variables were eliminated. Within this reduced dataset, 64% or 32/50 were designated as higher prescribers and 36% (18/50) were designated as the lower prescribers and those least committed to using domperidone to treat LMS.

I used a fitted logistic regression model which treats each one of the levels of the independent variable as actual numbers. This approach provides flexibility in terms of interpreting the model's coefficients associated with the independent variables. However, it assumes an equal effect on the dependent variable from one level to another.

There were two significant associations in the dataset of midwives, one related to caseload size and the other to practice location. The results of the logistic regression indicate that:

- each level of increase on the ordinal scale of the midwives' caseload size (see Table 5) will make the midwife 4.76 times more likely to be a higher domperidone prescriber, while keeping the rest of the independent variables constant in the model (p = 0.009). (Effect: 4.76);
- a midwife whose practice location is outside Vancouver (See Table 4) is 6.67 (1/0.15) more likely to not be a higher domperidone prescriber, while keeping the rest of the independent variables constant in the model. (p = 0.03). (Effect: 0.15).

3.10.17 Key Findings from the Midwives' Survey

The Survey of BC Midwives gathered self-reported information on the personal, caseload, treatment and prescribing characteristics of licensed and practising midwives in BC who used domperidone to treat their patients who had LMS.

The midwives were predominantly female and the majority had been practising for less than ten years; almost 80% had ten clients or less on their caseloads with LMS in the past year. Two-thirds of the midwives were considered high prescribers (prescribing domperidone to 25% or more of their caseloads) and one-third low prescribers (prescribing domperidone to under 25% of their caseload).

Forty percent (40%) of the midwives had practices in the Lower Mainland and Vancouver while 60% practiced in other areas of the province including the Fraser Valley, Okanagan, Interior, Northern BC or in a rural area.

The methods most commonly used by midwives to determine LMS were a count of the baby's wet diapers and feedback from the mother on the baby's behaviour, for example, fussiness that the mother felt might indicate LMS. The least common method midwives used for assessing milk supply was test/retest weighing of the baby after feedings.

There was a strong consensus on the treatment approaches that midwives felt were most useful to treat LMS. The only approach not used by the majority of midwives was reducing supplementation.

The survey asked midwives to identify the sources of information they had found to be most useful for assessing the safety and effectiveness of domperidone when it is used to treat LMS. The three sources most highly rated by over 70% of the midwives were consensus statements by breastfeeding experts, information from professional associations and colleagues and the midwives' own personal clinical experience with the drug. Information from pharmaceutical companies was considered to be the least useful source, identified by 10% of the midwives.

The survey asked midwives to assess the frequency with which they implemented three types of patient assessments prior to recommending or prescribing domperidone. Over 85% took the patient's personal and cardiac history and reviewed the patient's use of other QT-prolonging drugs on a frequent basis. The frequency of recommending a patient undergo an ECG was low, with about 90% rarely or never recommending this test.

The dose levels of domperidone most midwives recommended as being most effective to treat LMS were higher than the 30 mg/day recommended by Health Canada and the European Medicines Agency. Sixty percent (60%) of the midwives said that doses of 80 mg/day or more were needed to effectively treat LMS. The risks of domperidone are dose-related in an older age female population.

The Midwives' Survey measured only one outcome of the treatment of LMS using domperidone. This was the midwives' estimate of the percentage of clients who could exclusively breastfeed after treatment with domperidone without supplementation or donor milk. Almost 60% of the midwives estimated that domperidone treatment resulted in at least 50% of their clients being able to achieve this goal. However, how the midwives arrived at this estimate and how long exclusive breastfeeding lasted was not explored in the survey.

Over a third of the midwives said that 25% or more of their clients initiated a discussion of domperidone before they mentioned it as a potential treatment for LMS; just over 10% said that this never happened. All of the midwives who answered the survey question were aware of Health Canada's health advisories on domperidone although the majority felt that the advisories had limited applicability to those using domperidone to treat LMS. Ninety percent (90%) were also aware that using domperidone to treat LMS is an off-label use.

Over 80% of the midwives felt that domperidone poses no significant or minimal risks to their clients who are breastfeeding and 100% made this assessment for infants. However, when all opinions of the midwives were considered, 16% (9/56) were uncertain or felt they lacked information about the potential risks of domperidone to babies (Table 16).

Two open-ended questions addressed midwives' experiences with and views of domperidone. The most frequent theme reported was that some midwives believed that 30 mg/day of domperidone was not sufficient for treating LMS. Other major themes were that domperidone should not be the first approach to addressing LMS and that a wider analysis of the mother's circumstances and needs should be undertaken and that more research is required on the use of domperidone as a galactogogue. Results of the logistic regression concluded that the higher the midwives' caseload of clients with LMS, the more likely they were to prescribe domperidone to a higher percentage of clients and that midwives who practiced outside of Vancouver were less likely to prescribe domperidone than those practicing in Vancouver and the Lower Mainland.

3.11 Findings from the Physicians' Survey

3.11.1 Contents of this Section

This section presents the findings from the analysis of data from the survey of BC family physicians who provided postpartum care to at least two patients in the past year. Sections 3.11.2 – 3.11.17 report the results of the bivariate analysis using chi-square and the Fisher's Exact Test to measure associations between the dependent and independent variables. The results of the post-hoc pairwise analysis and the multiple logistic regression are reported in Section 3.11.18. A summary of key findings from this section is presented in 3.11.19. This section also includes an analysis of the qualitative comments of physicians on aspects of prescribing domperidone and treating LMS.

3.11.2 Physicians' Survey Measurement Variables

Two dependent variables were considered in the analysis of the physicians' survey results. One dependent variable was used for the questions that applied to all clinicians and addressed whether or not they prescribed domperidone to treat LMS and some of their approaches to treating LMS. Among the family physicians, 90.3 % (147/161) prescribed domperidone and 8.7% (14/161) did not.

The other dependent variable applied only to the physicians who prescribed domperidone and was used for questions on the survey that applied to this group. This dependent variable measured the frequency with which the physicians prescribed domperidone to patients on their caseload who had LMS. This was the same dependent variable used to analyze the midwives' results (see Section 3.4). Each of these dependent variables was measured in association with the appropriate independent variables included in the survey questions.

3.11.3 Physicians' Survey Participation Level

One hundred and eighty-six (186) family physicians opened the survey link. Of these, 11.3% (21/186) did not proceed with the survey and 1.6% (3/186) did not qualify because they did not meet the inclusion criteria. Of those who opened the link, 87.1% (162/186) started the survey. One of these participants completed three questions or less; these results were not included. This left a baseline group for the analysis consisting of 161 physicians.

I estimated being able to achieve a completed sample size of 274 family physicians based on the original population parameters and numbers of family physicians in the areas I selected. However, despite including all the FPDs from my original population in my outreach and using multiple survey invitations and reminders transmitted through the FPDs, I was unable to achieve my target sample size.

3.11.4 Physicians' Personal and Practice Characteristics

Almost 95% of family physicians identified their gender in the survey. The majority of physicians (76.3% or 116/152) identified as female; 23.7% (36/152) identified as male. These results suggest that there might have been an over-representation of female physicians participating in the survey. Data from the Canadian Institute for Health Information found that in 2018, 42.1 % of physicians in Canada were female (190) but this includes both family and specialist physicians. It is possible that a higher percentage of female physicians are involved in postpartum care or breastfeeding issues and might have been more motivated to participate in the survey, however this could not be confirmed. There was no statistical association between the gender of physicians responding to the survey and whether or not they prescribed domperidone ($p = 0.266$).

Survey participants were members of fourteen different Family Practice Divisions, which represented four Family Practice geographical divisions (See Table 17). A quarter of the practicing physicians were from Vancouver and the Lower Mainland. There was no association between the FPD region of physicians and whether or not they prescribed domperidone when regional results were considered or clustered into Vancouver/Lower Mainland and outside of this area.

Table 17: Family Practice Regions of Family Physicians*

Family Practice Regions	Number of FPDs	Total	Prescribed Domperidone	Did Not Prescribe Domperidone
	14	149 100.0%	137 100.0% 91.9%	12 99.9% 8.1%
Vancouver and Lower Mainland	2	36 24.2%	32 23.4% 88.9%	4 33.3% 11.1%
Fraser Region	7	65 43.6%	58 42.3% 89.2%	7 58.3% 10.8%
Interior Region	2	16 10.7%	15 10.9% 93.8%	1 8.3% 6.2%
Vancouver Island	3	32 21.5%	32 23.4% 100.0%	0 0.0% 0.0%

Fisher's Exact Test: $p = 0.2093$
*No location provided = 12

The time that physicians had been in practice ranged from under ten to over 30 years. Half of the physicians (80/158) had practiced less than 10 years, about a third (51/158) had practiced for twenty years or more and 17.1% (27/158) had been in practice between 10-19 years. There was no association between the length of time a physician had been in practice and whether or not they prescribed domperidone ($p = 0.711$)

3.11.5 Prevalence of LMS on Physicians' Caseload

Results from the physicians' survey indicated that 18% had over twenty patients with LMS on their caseloads in the past year but 45% had less than five patients or none. No data was available which indicates how common LMS was among the total caseload. There was a significant association between the number of patients on a physician's caseload being treated for LMS and whether or not the physician prescribed domperidone (see Table 18).

Table 18: Estimated Number of Patients with LMS on Physicians' Caseloads

Estimated Number of Patients with LMS on Physicians' Caseload in Past Year	Total	Prescribed Domperidone	Did Not Prescribe Domperidone
	161	147	14
Over 20	29 18.0%	27 (18.4%) (93.1%)	2 14.3% 6.9%
11-20	20 12.4%	20 13.6% 100.0%	0 0.0% 0.0%
6-10	40 24.8%	38 25.9% 95.0%	2 14.3% 5.0%
1-5	69 42.9%	61 41.5% 88.4%	8 57.1% 11.6%
None	3 1.9%	1 0.7% 33.3%	2 14.3% 66.7%

Fisher's Exact Test: $p = 0.0250$

3.11.6 Approaches Physicians Use to Assess LMS

The survey asked physicians to describe how frequently they used six commonly used approaches to assess whether their clients had LMS. The approaches included evidence-based methods such as test weighing and reweighing of the breastfeeding infant over a twenty-four-hour period and qualitative methods such as the physician relying on the mother's reports of baby cues such as fussiness which she could interpret as hunger. Results in Table 19 indicate that the most frequently used approach by family physicians to assess LMS involved the tracking of an infant's weight on a growth curve. Reliance on a mother's report of a baby's behavioural cues and the mother's own reports of lack of milk were used frequently or all of the time by over 80% of the physicians. The approach used least frequently was the test/retest weighing of babies after feeding; only 30% of the physicians said that they used this approach frequently (see Table 19). Each of these approaches was examined to see if there was any association between the methods and whether or not the physician prescribed domperidone; no significant associations were found. The *p*-values for these measures are reported in Table 19.

Table 19: Approaches Physicians Use to Diagnose LMS

Methods	Total	Use Frequently/ Most of the Time	Use Half the Time/Once in a While	Never Use	*p*-values
Test/test of baby weight	161 100.0%	47 29.2%	60 37.3%	54 33.5%	0.4987
Mother's assessment of baby cues	161 100.0%	132 82.0%	26 16.1%	3 1.9%	1.000
Measurement of breastmilk volume	159 100.0%	52 32.7%	60 37.7%	47 29.6%	0.5295
Mother's reports of lack of milk	160 100.0%	130 81.2%	26 16.3	4 2.5%	0.0603
Number wet diapers/day	160 100.0%	112 70%	41 25.6%	7 4.4%	0.4094
Tracking of baby weight on growth curve	159 100.0%	151 95.0%	7 4.4%	1 0.6%	1.000

3.11.7 Approaches Physicians Use to Treat LMS

The survey asked family physicians to identify the approaches that they used to treat their patients who have LMS from a check-list of eight different methods. The three most common methods physicians said that they used to treat LMS were recommending that the mother increase the frequency of breastfeeding or pumping, providing information about effective lactation techniques and prescribing domperidone. Less than half of the physicians reported using non-prescription galactogogues to increase milk supply.

All of the methods, excluding the prescribing of domperidone, were measured in relation to whether or not domperidone was prescribed to determine whether specific methods could be linked to prescribing the drug. No statistical association was found with any of these approaches (see Table 20).

Table 20: Approaches Family Physicians Used to Treat LMS

Treatment Approaches	Total	Used Approach	Did Not Use Approach	*p*-values
Increase frequency of breastfeeding or pumping	161 100%	153 95.0%	8 5.0%	0.5252
Reduce supplementation	161 100%	58 36.0%	103 64.0%	0.3824
Provider information on lactation techniques	161 100%	141 87.6%	20 12.4%	1.000
Provider information about lactation	161 100%	137 5.1%	24 14.9%	1.000
Discuss impact of birth and breastfeeding	161 100%	85 52.8%	76 47.2%	0.1803
Recommend non-prescription galactogogues	161 100%	74 46.0%	87 54.0%	0.0895
Refer patient to lactation consultant/expert	161 100%	142 88.2%	19 11.8%	1.000
Prescribe or recommend domperidone	161 100%	147 91.3%	14 8.7%	1.000

3.11.8 Physician Comfort Addressing Breastfeeding Problems

Specialized training for family physicians on addressing breastfeeding problems is limited. I included a question in the survey asking physicians how comfortable they were addressing breastfeeding problems to determine if comfort levels were associated with domperidone prescribing.

Only 36.0% of the physicians described themselves as being very comfortable addressing breastfeeding problems with just over 10% saying they were not very comfortable or not comfortable at all. These results were measured in relation to whether or not a physician prescribed domperidone and a significant association was found (see Table 21).

Table 21: Physician Comfort Addressing Breastfeeding Problems

Comfort Levels	Total	Prescribed Domperidone	Did Not Prescribe Domperidone
	161	147	14
Very comfortable	58 36.0%	58 39.5% 100.0%	0 0.0% 0.0%
Somewhat comfortable	86 53.4%	78 53.1% 90.7%	8 57.1% 9.3%
Not very comfortable	15 9.3%	10 6.8% 66.7% 6.2%	5 35.7% 33.3% 3.1%
Not comfortable at all	2 1.2%	1 0.7% 50.0%	1 7.1% 50.0%

Fisher's Exact Test: $p = 0.0001$

3.11.9 Information Sources Physicians Considered Most Useful

The survey asked physicians to identify the information sources they found most useful in terms of providing information about the effectiveness and safety of domperidone to treat LMS. This survey question was directed to physicians who were prescribing the drug. Information sources included Cochrane or other independent systematic reviews, consensus statements from experts, and online sources.

The three types of information sources considered most useful, by over 60% of the physicians, were advice from colleagues, consensus statements by experts and online/internet information. Less than a third of the physicians identified Cochrane and other systematic reviews, the highest evidence-based source, as a 'most useful' information source (see Table 22).

Table 22: Information Sources Physicians Considered Most Useful

Information Source	Total	Information Source Considered Useful	Information Source Not Considered Useful	Ranking	*p*-values
Advice from Colleagues	147	97 66.0%	50 34.0%	1	0.555
Consensus Statements from Breastfeeding Experts	147	91 61.9%	56 38.1%	2	0.332
Online/Internet Sources	147	89 60.5%	58 39.5%	3	0.966
Personal Clinical Experience with the Drug	147	86 58.5%	61 41.5%	4	0.040
Patient Feedback	147	85 57.8%	62 42.2%	5	0.048
Workshops/ Seminars/ Lectures	147	55 37.4%	92 62.6%	6	0.893
Health Canada Safety Reviews/ Advisories	147	47 32.0%	100 68.0%	7	0.999
Cochrane/ Independent Systematic Reviews	147	45 30.6%	102 69.4%	8	0.017
Information from Professional Associations/ Colleges	147	39 26.5%	108 73.5%	9	0.742
Other Research in the Medical Literature	147	37 25.2%	110 74.8%	10	0.690
Textbooks on Breastfeeding	147	24 16.3%	123 83.7%	11	0.958
CPS	147	10 6.8%	137 93.2%	12	1.000
Information from Drug Manufacturers	147	5 3.4%	142 96.6%	13	0.5845

There were two sources of information about domperidone's effectiveness and safety where there was a significant association between the type of information identified by physicians and the level of physician prescribing of domperidone to patients with LMS. These were Cochrane or other independent systematic reviews (Table 23) and patient feedback (Table 24).

Table 23: Systematic Reviews as a Useful Source of Information*

Cochrane or Other Independent Systematic Reviews	Total	Higher Prescribers	Lower Prescribers
	146	115	31
Yes	45 30.8%	30 26.1% 66.7%	15 48.4% 33.3%
No	101 69.2%	85 73.9% 84.2%	16 51.6% 15.8%

Chi-square: $p = 0.017$
*NR = 1

Table 24: Patient Feedback as a Useful Source of Information*

Patient Feedback	Total*	Higher Prescribers	Lower Prescribers
	146	115	31
Yes	84 57.5%	71 61.7% 83.5%	13 41.9% 15.3%
No	62 42.5%	44 38.3% 71.0%	18 58.1% 29.0%

Chi-square: $p = 0.048$
*NR = 1

In an open-ended question, eight family physicians who prescribed domperidone identified one or more information sources that they had found most useful for assessing domperidone's safety and efficacy. Four of the eight physicians identified the website and information provided through the Canadian Breastfeeding Foundation coordinated by Dr. Jack Newman. Individual family physicians also identified the Goldfarb Breastfeeding Centre, the Academy of Breastfeeding Medicine, local lactation consultants, public health personnel and LactNet as useful information sources about domperidone.

3.11.10 Patient Assessments Conducted by Physicians

Domperidone is a QT-prolonging drug that has been associated with potential cardiac risks such as serious arrhythmias and Torsades de Pointes. For this reason, specific medical assessments

prior to prescribing the drug are recommended. These include physicians assessing the patient's personal and family cardiac history, his/her current use of other QT-prolonging drugs and, in some cases, ordering an ECG.

Although over 80% of physicians took patients' cardiac histories and assessed their patient's use of other QT-prolonging drugs, most rarely or never ordered an ECG. Fifteen percent (15%) of the physicians said that they rarely or never collected information on a patient's cardiac history or assessed their use of other QT-prolonging drugs (see Table 25).

Table 25: Patient Assessments Conducted by Physicians

Test	Total	Use Always/Most of the Time	About Half the Time	Once in a While/Never	*p*-values
Taking patient/family cardiac history	146	120 82.2%	3 2.1%	23 15.8%	1.000
Assessing patient use of other QT-prolonging drugs	147	120 81.6%	5 3.4%	22 15.0%	0.560
ECG	145	21 14.5%	9 6.2%	115 79.3%	0.018

The frequency of ordering these tests was measured in relation to the level of domperidone prescribing on the physicians' caseloads and one association was found. This was between how frequently physicians ordered an ECG and how frequently they prescribed domperidone to patients on their caseloads who had LMS (see Table 26).

Table 26: Physician Ordering of ECG and Prescribing Levels*

Frequency of Ordering ECG	Total	Higher Prescribers	Lower Prescribers
	145	114	31
Always/most of the time	21 14.5%	12 10.5% 57.1%	9 29.0% 42.9%
About half the time	9 6.2%	9 7.9% 100.0%	0 0.0% 0.0%
Once in a while/never	115 79.3%	93 81.6% 80.9%	22 71% 19.1%

Fisher's Exact Test: $p = 0.0182$
*NR = 2

3.11.11 Dose Levels of Domperidone Recommended by Family Physicians

Eighty-four percent (84%) (123/147) of the family physicians provided specific information on the dose levels of domperidone they believed were most effective in treating LMS. The question was phrased indirectly in order to avoid sensitivity bias. The question was asked only to physicians who prescribed the drug for LMS. This question assessed four levels of prescribing, including 30 mg/d and above. A maximum daily dose of domperidone of 30 mg/day is recommended by Health Canada and the European Medicines Agency (124, 170) as the safest level of prescribing.

Almost forty percent (40%) (49/123) of the physicians considered 30 mg/day as the most effective dose of domperidone to treat LMS, 30.1% (37/123) considered 60 mg/day to be most effective and 30.1% (37/123) of the physicians recommended doses of 80 mg/day or more.

There was no significant association between these specific dose level recommendations and the frequency with which physicians prescribed domperidone on their caseloads. However, when the data was clustered into two categories – within the prescribing guidelines of 30 mg/day and above the prescribing guidelines, there was a significant association between the dose levels and the frequency with which physicians prescribed domperidone to patients on their caseload with LMS (see Table 27).

Table 27: Dose Levels of Domperidone Recommended by Physicians*

Dose levels	Total*	Higher Prescribers	Lower Prescribers
	123	96	27
Within guidelines (maximum 30 mg/day)	49 39.8%	33 34.4% 67.3%	16 59.3% 32.7%
Above guidelines (more than 30 mg/day)	74 60.2%	63 63.6% 85.1%	11 40.7% 14.9%

Chi-square: $p = 0.01963$
*NR = 4
Other comments = 20 (see below)

Twenty respondents had other comments about dose levels which did not fall into the categories listed in the table. Nine physicians said that the dose levels they prescribed were variable. Six physicians said they recommended 40 mg/day; three said the dose depended on the patient and two of the physicians provided no specific data on dose levels.

3.11.12 Physicians' Estimate of Domperidone's Impact on Breastfeeding

The survey asked physicians to estimate the degree to which they believed that domperidone helped their patients with LMS to breastfeed without supplementation or donor milk. The intention to

exclusively breastfeed is a common goal for mothers who plan to breastfeed. This question was asked only to those physicians who had prescribed domperidone.

Seventy percent (70%) of the physicians said that domperidone had helped 50% or more mothers on their caseload to exclusively breastfeed. How consistently this outcome was measured and at what point of time during the lactation process is unknown. There was no statistical association between the physician's estimates of exclusive breastfeeding after domperidone use and the degree to which they prescribed domperidone to their patients (See Table 28).

Table 28: Physicians' Assessment of Domperidone's Impact on Breastfeeding*

Exclusive breastfeeding after domperidone use	Total*	Higher Prescribers	Lower Prescribers
	130	109	21
Almost all (over 75%)	20 15.4%	18 16.5% 90.0%	2 9.5% 10.0%
Many (50-74%)	71 54.6%	62 56.9% 87.3%	9 42.9% 12.7%
Some (25-49%)	33 25.4%	24 22.0% 80.0%	9 42.9% 20.0%
A few (under 25%) or None	6 4.6%	5 4.6% 66.7%	1 11.8% 33.3%

Fisher's Exact Test: $p = 0.2287$
*NR = 4
Uncertain = 13

3.11.13 Physicians' Estimate of Who Initiated Discussions on Domperidone

Research indicates that patients can influence physicians' prescribing decisions (9, 56, 60). Physicians were asked to estimate how frequently their patients initiated a discussion of domperidone. Patients initiating these discussions was relatively common. Over a quarter of the physicians (27.2% or 43/158) said that over half of their patients had initiated a discussion of domperidone to treat LMS. A third (33.5%, 53/158) said that between 25 – 50% of their patients had initiated these conversations and 36.1% (57/158) said that it occurred among less than 25% of their patients. Only 3.2% (5/158) of the physicians reported that it never happened. There was no statistical association between the frequency with which patients-initiated discussions about domperidone and whether or not the physician prescribed domperidone ($p = 0.241$).

3.11.14 Physician Knowledge of Domperidone's Off-label Status

The vast majority of physicians, 94.4% (135/143), identified the use of domperidone to treat LMs as an off-label use; 5.6% (8/143) considered it to be an approved use. However, 10.1% (16/159) of the physicians who addressed the question were uncertain of the drug's approval status. There was no statistical association between the physicians' knowledge of domperidone's approval status and whether or not they prescribed domperidone (p = 1.000).

3.11.15 Physicians' Response to Health Canada Advisories

Drug advisories are a key risk communication tool used by Health Canada to inform healthcare professionals and the public about drug risks. Health Canada issued two advisories about domperidone in 2012 and 2015. Both advisories focused on the approved uses of domperidone and the cardiac risks associated with its QT-prolonging potential. The advisories recommended a maximum daily dose of 30 mg/day and the use of the drug for a short duration.

The majority of physicians, 86.2% (137/159), were aware of one or more of these advisories; 13.8% (22/159) said they did not know about them. Results in Table 29 indicated that over 65% of physicians considered the health advisories to be of limited applicability to their off-label use of domperidone to treat LMS. Less than 10% of the physicians found the advisories to be fully applicable. There was no statistical association between physician prescribing of domperidone and their awareness of these advisories or whether they considered them applicable.

Table 29: Physicians' View of the Applicability of Health Canada Advisories

Applicability of Health Canada advisories	Total*	Prescribed Domperidone	Did Not Prescribe Domperidone
	156	142	14
Fully applicable	13 8.3%	10 7.0% 76.9%	3 21.4% 23.1%
Quite applicable	38 24.4%	34 23.9% 89.5%	4 28.6% 10.5%
Somewhat applicable	70 44.9%	67 47.2% 95.7%	3 21.4% 4.3%
Not applicable	35 22.4%	31 21.8% 88.6%	4 28.6% 11.4%

Fisher's Exact Test: $p = 0.1139$
*NR = 5

3.11.16 Physicians' Assessment of Domperidone's Risks to Mothers and Infants

Survey results indicate that almost 80% of physicians considered that domperidone posed minimal or no significant risks to mothers who are breastfeeding. Seven physicians were uncertain about the risks. There was a significant association between physician's assessment of the risks of domperidone to patients and whether or not they prescribed domperidone (see Table 30).

Table 30: Physicians' Assessment of Domperidone's Risks to Patients*

Assessment of Risk to Patients	Total*	Prescribed Domperidone	Did Not Prescribe Domperidone
	151	141	10
No significant risks	7 4.6%	7 5.0% 100.0%	0 0.0% 0.0%
Minimal risks	113 74.8%	110 78.0% 97.3%	3 30.0% 2.7%
Moderate risks	25 16.6%	21 14.9% 84.0%	4 40.0% 16.0%
Significant risks	6 4.0%	3 2.1% 50.0%	3 30.0% 50.0%

Fisher's Exact Test: $p = 0.0006$
*NR = 3
Uncertain = 7

Table 31 indicates that over 90% of the physicians who rated the level of risk believed that domperidone posed minimal or no significant risks to infants. However, when all the responses were considered, 13.3% (21/158) said they were uncertain about the risks to infants. The association between physicians' estimates of the risk of domperidone to infants and whether or not the physician prescribed domperidone also showed a significant statistical association (see Table 31).

Table 31: Physicians' Assessment of Domperidone's Risk to Infants*

Assessment of Risks to Infants	Total*	Prescribed Domperidone	Did Not Prescribe Domperidone
	137	129	8
No significant risks	57 41.6%	57 44.2% 100.0%	0 0.0% 0.0%
Minimal risks	72 52.6%	68 52.7% 94.4%	4 50.0% 5.6%
Moderate risks	6 4.4%	3 2.3% 50.0%	3 37.5% 50.0%
Significant risks	2 1.5%	1 0.8% 50.0%	1 12.5% 50.0%

Fisher's Exact Test: $p = 0.0001$
*NR = 3
Uncertain = 21

3.11.17 Physicians' Experiences with Domperidone

An open-ended question asked all physicians for their general comments or recommendations related to the use of domperidone to address LMS. Over 20% (22.4% or 36/161) made open-ended comments which were analyzed using a four-state thematic coding process.

The first stage involved categorizing comments into clusters of comparable themes (e.g., safety concerns) in order to develop more succinct theme labels. Clustered comments were reviewed within the categories to clarify consistency and reassigned as needed and to clarify category labels. Comments were then recoded using these draft labels to determine the appropriateness of fit. Comments were then moved or recoded again using the final category labels in order to establish internal consistency within the coding categories. Finally, blind coding was done categorizing all the comments again within the coding categories. The results were compared to the three previous coding processes and adjustments were made in the classification of comments.

The final coding labels were based on eight overarching theme categories with the following number of comments by physicians: domperidone effectiveness (9), Health Canada warnings (3), patient needs (6), benefits (8), physician education (1), role of other healthcare providers (5), safety (24), and issues related to LMS (2). Some physicians made multiple comments.

The comments made by the largest group of physicians were on issues related to the safety of domperidone when used to treat LMS. Within this category, ten respondents talked about their concerns about its risks and, in some cases, their reluctance to prescribe it. Four (4) respondents

believed that there were fewer risks of domperidone use for younger women although these risks still had to be taken into account. Two respondents felt that the risks of a mother taking other QT-prolonging drugs were critical to consider prior to prescribing. One respondent recommended that domperidone only be used for a short duration,

> " . . . the risk depends on the individual patient. Overall, this population tends to be younger and without cardiac or liver comorbidities, so it is a lower risk population than the general population – but the risk is still there . . . . "

> "I always worry about side effects, especially QT prolongation, when prescribing it."

Four of the physicians said that the risks of domperidone should be explained in detail to patients in an informed consent process and three said that conducting patient assessments and tests prior to prescribing were critical:

> "Medication and hx (history) review needs to be addressed for all patients – so those who may incur risk are cautioned and evaluated appropriately."

Nine physicians had comments about the effectiveness of domperidone. Three said that the evidence of domperidone's effectiveness was poor but six said that the effectiveness of the drug depended on variables such as the patients' needs and the dose levels prescribed.

> "I can't estimate a recommended dose – (there is) no conclusive evidence it works."

> "Guidelines often recommend short term (e.g., two weeks) of use but I find most patients need longer or they find (their) supply drops when they stop."

Eight respondents described the benefits of domperidone use saying that it was effective and was the only pharmacologic solution available for a difficult health condition:

> "Other than lifestyle changes and fenugreek, it's our only shot at Rx solutions. Often patients get desperate and want to try anything to help with milk supply despite Health Canada warnings and limited evidence behind it."

Six comments were related to patient needs, primarily how concerned women with LMS were to find a treatment that helped them increase their milk supply. The needs of mothers often led to them suggesting taking the drug prior to their physicians mentioning it. For one physician domperidone use,

" . . . can be short-term use only to allay mother's fears/concerns, often Rx supplied with reassurance and advice and the Rx is not filled by patient."

Five physicians spoke about healthcare providers recommending domperidone, one saying:

"Patients really want this – although no evidence . . . it is the patients that want it and their midwives recommend it and so do the maternity groups."

One physician said that pharmacists are often reluctant to fill prescriptions for more than 30 mg/day. Three physicians spoke about the impact of the Health Canada advisories on domperidone. Two said that they had changed their practice since the warnings and reduced the dose they prescribed and one said that the warnings had increased the anxiety of their patients.

One physician said that there needed to be a better understanding of LMS before treatment is started. Another noted that if a mother uses domperidone for their first child they are likely to use it for their subsequent babies.

3.11.18 Further Analysis of Findings from the Physicians' Survey

This section provides the results of a further analysis of the data using a post-hoc pairwise analysis among the multiple levels of the given independent variables followed by the results of the logistic regression to determine the direction and meaning of any significant associations.

The post-hoc pairwise analysis applied to tables with more than two levels and used an adjusted Fisher's Exact Test with a confidence level of $p < 0.1$. Two dependent variables were used to analyze the physicians' data: whether or not a physician prescribed domperidone (calculated for all the respondents) and the level at which physicians prescribed domperidone to patients with LMS (calculated only for those who prescribed domperidone).

The post-hoc pairwise analysis of the physicians' data indicated the following relationships between the levels of the dependent binary variable of prescribers/non-prescribers of domperidone and the corresponding independent variables. Tables with independent binary variables were not included in this analysis

- **Table 21: Physicians' Comfort Handling Breastfeeding Problems**. The levels of very comfortable and not very comfortable were related to whether or not the physician prescribed domperidone with an adjusted $p = 0.0012$.
- **Table 30: Physicians' Assessment of Domperidone's Risk to Patients.** The levels of minimal risks and significant risks were related to the prescribing of domperidone with an adjusted $p = 0.00828$.
- **Table 31: Physicians' Assessment of Domperidone's Risk to Infants.** The levels of no significant risks/moderate risks and minimal risks/moderate risks were related to the prescribing of domperidone with adjusted $p = 0.00302$ and $p = 0.04880$, respectively.

The post-hoc pairwise analysis indicated the following relationships between the dependent binary variable of higher and lower prescribers of domperidone to patients with LMS on the physician's caseload and the following independent variables.

- **Table 18: Estimated Number of Patients with LMS on Physician's Caseload**. The pair of levels 11-20 and none were somewhat related to the prescribing of domperidone with an adjusted $p = 0.119$.
- **Table 26: Frequency that Physicians Order an ECG.** The levels of always/half and always/once in a while were related to domperidone prescribing levels at adjusted $p = 0.0867$ and $p = 0.0732$, respectively.

The logistic regression was based on the analysis of the two physician datasets involving the two dependent variables. These were whether or not physicians prescribed domperidone and, for prescribers only, the level at which they prescribed the drug to patients on their caseloads.

The first step in developing the logistic regression model was to remove missing dependent and independent variables from the datasets: reducing the dataset of all physicians from 161 to 135 and from 147 to 121 cases for the prescriber only group.

I used a fitted logistic regression model which labels each of the levels with equidistant numbers. For example, in terms of the physician's comfort with breastfeeding issues, the labels were: (1) not at all comfortable, (2) not very comfortable, (3) somewhat comfortable, (4) very comfortable. This approach provides flexibility in terms of interpreting the model's coefficients associated with the independent variables, however, it assumes an equal effect on the dependent variable from one level to another. Table 32 shows the results of the logistic regression for the physicians' survey data with a discussion of the direction of the significant associations following the table.

Table 32: Physicians' Survey: Results of Logistic Regression

Dependent Variable: Whether or not physician prescribed domperidone	**Effect**	***p*-values**
Independent Variables		
Physician's comfort with breastfeeding issues (Table 21)	8.41	0.02
Physician's assessment of domperidone's risk to infants (Table 31)	0.13	0.008
Dependent Variable: Level of prescribing of domperidone (prescribers only)		
Cochrane systematic review as a useful information source (Table 23)	0.31	0.02
Dose level of domperidone: within and above guidelines (Table 27)	3.81	0.007

This analysis concluded that:

- Each level of increase on ordinal scale of the physician's comfort with breastfeeding issues will make the physician 8.41 times more likely to prescribe domperidone than not to prescribe it.
- Each level of increase on the ordinal scale of the physician's assessment of domperidone's risk to infants (from lower to higher) will make the physician 7.69 times more likely to not prescribe domperidone than to prescribe it.
- A physician who identifies Cochrane or other independent systematic reviews as a useful information source is 3.22 times more likely to not be a higher domperidone prescriber than to be one.
- A physician who prescribes domperidone above the guidelines of 30 mg/day is 3.81 times more likely to be a higher domperidone prescriber to patients with LMS on their caseload than be a lower prescriber.

3.11.19 Summary of Key Findings from the Physicians' Survey

The Physician's Survey gathered information on the practice, treatment and prescribing characteristics of family physicians in BC who provided postpartum services to at least two patients in the past year. One hundred and sixty-one (161) family physicians participated in the survey; 91.3% (147/161) prescribed domperidone and 8.7% (14/161) did not. Both groups were included in the survey analysis. There was no significant association between the gender of the family physicians, their time in practice and location and whether or not they had prescribed domperidone.

Eighteen percent (18%) of the physicians had over 20 patients who with LMS on their caseload but the largest majority (42.9%) had 1 – 5. Results indicated that the most common method physicians used to assess LMS was the tracking of a baby's weight on a growth curve; the least used method was the test/retest of a baby's weight after feeding. The most common method used by physicians to treat LMS was recommending an increase in breastfeeding or pumping. Prescribing domperidone was the second most common approach that physicians cited.

Because most family physicians do not receive specialized training in addressing breastfeeding problems, the survey asked respondents to describe their degree of comfort in handling these types of health issues. Only 36% of the physicians said they felt very comfortable addressing breastfeeding problems. Physicians who prescribed domperidone were also asked to identify the information sources that they found most useful in terms of providing information about domperidone's effectiveness and safety. The three types of information sources that were cited most frequently were advice from colleagues, consensus statements on domperidone and online or internet sources of information.

Over 80% of the family physicians took the cardiac history of patients and their use of other QT-prolonging drugs frequently or most of the time but only 14.5% (21/145) said they ordered ECGs

frequently. Most physicians prescribed domperidone above the recommended level of 30 mg/day. Only forty percent (40%) (49/123) of the physicians said that their recommended dose of domperidone was 30 mg/day while 30% (37/123) recommended doses of 80 mg/day or higher.

One of the measures of domperidone's effectiveness is the degree to which it helps mothers exclusively breastfeed. Seventy percent (70%) (91/130) of the physicians estimated that at least 50% of their patients treated with domperidone were able to achieve this goal. However, the survey did not collect information on how and when this conclusion was arrived at.

Survey results suggest that patients initiate discussions about using domperidone to treat LMS before their physicians do. A quarter of the physicians (43/153) said that over half of their patients had initiated discussions about using domperidone before they did.

The vast majority of physicians identified the use of domperidone to treat LMS as an off-label use, however, 10% were uncertain about the drug's status. Over 85% (137/159) of the physicians were aware of one or more of Health Canada's warnings about domperidone's safety but most (105/156) felt that the advisories were of limited or no applicability when domperidone was used to treat LMS. Over 80% of the physicians did not believe that domperidone posed many risks to their patients or their infants.

The bivariate analysis using chi-square or the Fisher's Exact Test identified eight variables where there was a significant association between one of the dependent variables and the corresponding independent variables although the direction of this association was not established. Four significant findings emerged from the logistic regression of the physicians' survey data which showed associations between the dependent and independent variables and established the direction of these findings. The more comfortable physicians were with addressing breastfeeding problems with their patients, the more likely they were to prescribe domperidone than not to prescribe it. The higher that physicians estimated the risk of domperidone to infants, the less like they were to prescribe the drug. Physicians who considered Cochrane and other independent systematic reviews to be a useful information resource, prescribed domperidone less frequently to patients on their caseload. Finally, those who prescribed domperidone over the dose level of 30 mg/day were more likely to prescribe domperidone to a higher percentage of the patients on their caseloads.

4.0 FINDINGS FROM THE INTERVIEWS WITH MOTHERS

4.1 Introduction and Organization of this Chapter

The goal of this research was to examine the clinician, patient, policy and socio-cultural factors that may have contributed to the increasing off-label prescribing of domperidone to treat low milk supply (LMS) in British Columbia, Canada. I developed a 'socio-ecological model' as my conceptual framework to address these questions. This model identified the levels and variables in each level which could be contributing to this off-label use.

This chapter describes the methodology and results of the open-ended, semi-structured qualitative interviews with 18 mothers who breastfed their infants and were prescribed domperidone to manage their perceived problems with LMS. The interviews explored potential variables at four levels of the SEM: patient, community, institutional and socio-cultural. The interviews were held in between January and March 2018.

In this chapter I have used the term "mothers" and "she/her/hers" for all the participants who identified as cisgender females. I want to acknowledge, however, that individuals identifying otherwise may also be lactating parents.

The questions included on the interview guide were designed to be congruent with many of the content areas explored in the physicians' and midwives' surveys and that related indirectly to some areas of policy. This chapter provides information about the selection and recruitment of mothers for the interviews, the informed consent process, the development and implementation of the interview schedule, how data confidentiality was protected, the methods used to analyze the data and the findings that emerged from the interviews. The areas discussed with mothers and reported in the findings are:

- the mother's pregnancy, birth and hospital experiences;
- the mother's family background in relation to breastfeeding and current support for breastfeeding from partner;
- her expectations of breastfeeding and assessment of her breastfeeding experiences;
- source, type (e.g., person-to-person or classroom style) and perceived value of breastfeeding information and support pre- and post-birth including the mother's views on the gaps and limitations in services and support;
- how and when LMS was assessed and diagnosed;
- the treatment approaches mothers used to address LMS;

- the mother's knowledge of domperidone prior to using it, her awareness of its off-label status and her expectations of the drug;
- who prescribed domperidone, the dose levels used and duration of use;
- the mother's view of the effectiveness of domperidone for increasing her milk supply;
- other factors that influenced the mother's experiences with LMS and domperidone.

4.2 Development, Piloting and Implementation of the Interview Guide

A formal interview guide was developed to provide guidance in terms of the interview topics and ensure consistency between each of the interviews (See Appendix II). Each of the broad topic areas in the guide were further defined by a listing of specific prompts and follow-up questions. Questions were developed with the help of the members of my PhD advisory committee, including the input of a medical anthropologist with expertise in ethnographic research and the researcher who completed the first study on the rising use of domperidone to address LMS in BC (1). A lactation consultant, nurse, physician specializing in lactation issues and a La Leche counsellor also provided input into the development of the interview guide. They reviewed the final guide for question construction, understandability, relevance to the topic, sensitivity, flow, congruence, timeliness and potential bias.

A pilot interview was conducted with a mother with both breastfeeding experience and experience assisting women with LMS, some of whom were using domperidone. This pilot interview was focused primarily on assessing question flow and duration, testing the wording and understandability of questions, transitions between topics and the time needed to complete the interview. The first interview with a respondent included in the research was also treated as a pilot. It was intended that this interview would be discarded if problems arose during the interview that affected its quality, however, none arose so it was included in the results.

Prior to developing the interview guide, a limited literature review was undertaken to identify best practices associated with semi-structured qualitative interviews. These guidelines were incorporated into the development of the interview guide and implementation of the interviews (179, 191, 192).

4.3 Participant Inclusion Criteria, Sample Size, Recruitment and Selection

The four research inclusion criteria used to select mothers for the interviews included being a BC resident, having given birth to a baby who was full-term or near full-term (over 37 weeks) within the past year (calculated at the time of research participant selection), having used at least one prescription of domperidone to address LMS in the first six months after the baby's birth and the ability to speak and comprehend either English and/or French.

Mothers with preterm infants were not included in the research. This was because of the potential impact of preterm births on breastfeeding. Preterm babies often experience more significant health problems and these problems could affect their response to breastfeeding or a mothers' milk supply.

Up to 20 participants were projected as being included in the interviews. It was considered that this number would be of sufficient size to identify the experiences, perceptions and opinions of respondents who have used domperidone to treat LMS in order to avoid discovery failure and achieve data saturation.

In a study of sample size and saturation in PhD studies using qualitative data, Mason (193) found that the mean sample size, using different methods of calculation was 31. Another study, looking at optimum sample size in the commercial realm, found that 20 – 30 interviews were needed in order to uncover 90 – 95% of respondent needs and options (194). After the completion of 18 interviews, I felt that the increasing repetition of major themes and experiences within different contexts indicated a saturation point and that this number was sufficient to capture the range of the participant experiences with LMS and domperidone.

I used two methods to recruit participants for the interviews. Midwives and lactation consultants who attended an information meeting at UBC in April 2017 that reported the initial results of a systematic review on domperidone when used to treat LMS, were given information about the study at the meeting and were later contacted with a request to inform their clients about it. The majority of these attendees were from the Lower Mainland or Vancouver.

The second method used to recruit mothers included the posting of information about the study at BC Women's Hospital, and at several public health units in Vancouver where breastfeeding support meetings were held. This initial information described the purpose and sponsor of the study, the requirements of participants, provisions to protect confidentiality, information about a small gift card incentive and methods for contacting me for further information.

If mothers contacted me for further information about the research, I sent them a personal email including more details and clarified eligibility requirements. If they met these requirements and wanted to participate, I sent them a more detailed consent form to complete. It was evident, as information about the study began to circulate, that recruitment information was being more widely distributed by other healthcare providers, mothers and public health units.

Eighty-four (84) mothers with interest in the study contacted me by email between mid-January to mid-February 2018 to express interest in the study. Of these, almost 30% (25/84) did not meet eligibility requirements. Another 30% (26/84) were not needed after all the candidates were selected (their eligibility was not determined), 8% (7/84) did not provide further information about their eligibility and just over 30% (26/84) were eligible and placed in an eligibility pool.

Because I was concerned about whether my recruitment strategies would result in a sufficient number of participants, I decided there might be risks in using a random selection process. However, it was difficult to determine whether there was a selection bias in using the approach described above. Ultimately, there was a fairly good mix of age, background and location characteristics among the respondents who participated. The eligibility pool also ended up being small and several potential participants could not be contacted. Almost all of those in the eligibility pool group ended up participating in the interviews.

4.4 Informed Consent and Protection of Confidentiality

The research involved sending a consent form to the respondents who volunteered to participate in the research. The consent form provided information about the voluntary nature of the study, the study purpose, procedures and question topics, how the results would be used, potential risks and benefits of the study, incentives provided and how personal and data confidentiality would be protected.

Other methods for protecting the confidentiality and privacy of the participants who participated in the study included the following:

- data from the telephone interview audio files and hard copies of the transcripts were coded using a unique alpha-numeric code with no identifying information used;
- audio files were destroyed as soon as the typed transcripts were prepared. The transcripts were stored on a single use computer in the office of the co-investigator (primary research supervisor) and will be eliminated as soon as my PhD is completed;
- email and phone records of those who responded to the initial information about the interview but who did not participate were eliminated as soon interviews were completed;
- all of those who participated in the interviews requested a summary of the research results. I saved their names and contact emails on a list in a separate password-protected file kept on a server secured by UBC-IT on a single-use computer accessible only by me and delinked this with interview results. Participants agreed to my keeping these records for this purpose.

4.5 Data Analysis

Results were analyzed using a multi-stage thematic analysis approach that I adapted from the research literature (195 – 197). This involved clustering the interview data by codes and sub-codes into major themes related to the topic areas discussed. Codes were defined at the semantic level to stay close to the participants' expressed experiences. I used a manual coding process rather than coding software in order to facilitate my familiarity with all of the data, to reach a deeper understanding of the meaning of the data as well as to draw on my previous experiences with thematic analyses. Table 33 describes the steps involved in the codification process.

Table 33: Steps Used in the Thematic Analysis of Mothers' Interviews

Stage of Thematic Analysis	Tasks Included in the Analysis
Stage 1: Recording and transcribing the data, familiarization with the data	• Implementing and recording interviews • Transcribing each of the interviews into a written form using a professional transcription service - initial phase of data review • Checking the accuracy and completeness of transcriptions with the recorded interviews, where required • Reading the full transcript twice – using the broad topics in the interview guide to broadly categorize answers • Early identification of patterns and potential themes • Reviewing the transcripts again and preparing shorter transcripts for each interview to eliminate repetition and filler conversation (third reading)
Stage 2: Generating initial semantic codes and sub-codes and development of coding template	• Development of initial template for the consistent coding of data • Clustering the data into the template coding categories for two test transcripts to check fit and comprehensiveness • Reviewing and revising the template for accuracy and recategorizing data for the first two transcripts • Recording decision-making, problem areas and outliers
Stage 3: Coding of transcripts using template	• Clustering the data from all transcripts using the final coding template (fourth reading) • Considering validity of themes in relation to the entire dataset • Identifying and adding new codes to the template, if required • Selecting respondent comments to best illustrate key points made in the interviews
Stage 4: Further analysis and clustering of themes	• Development of theme analysis by extracting themes derived from the coding template for each transcript and entering the findings on separate summative data analysis sheets. This method provided an overview of the degree of duplication of central themes under each theme code and sub-code • Reviewing and summarizing theme clusters • Categorizing outliers • Identifying illustrative quotes

The following steps were taken to reduce bias and validate the findings from the interviews:

- I read each transcript four times and prepared an edited version of each transcript which removed conversational fillers, my questions and some repetition in order to prepare shorter, more accessible versions of the transcripts;
- when the transcripts were unclear and could not be verified by the audio recording, I re-contacted participants to ask for clarification;

- I monitored my own personal bias during the interview and focused on the words and experiences related by the respondents;
- I discussed my data interpretation and coding decisions with Dr. Vinay Kamat, a medical anthropologist and member of my research committee. He reviewed the coding decisions I made in relation to two interview transcripts for accuracy.

4.6 Findings from the Mothers' Interviews

4.6.1 Participant Characteristics

Eighteen (18) mothers who had used domperidone within the first six months of their baby's birth participated in the interviews. None of the woman were under 25 years old, three were from 25 – 30, the majority (ten) were 31 – 36 and five were 37 years of age or older. For 14 of the 18 women the baby being discussed in the interviews was their first and only child; four of the mothers had additional children. These four mothers had all tried to breastfeed their previous babies and described these breastfeeding experiences as "challenging" or "a struggle." Three of these mothers had used domperidone which they felt was helpful; one mother had stopped breastfeeding her previous baby without using domperidone. At the time of the interview, five of the respondents lived in Vancouver or the Lower Mainland, six lived in the Fraser Valley, five were from Vancouver Island and two lived in the interior of BC.

4.6.2. Family Support for Breastfeeding

The strength of the relationship between family and partner support and breastfeeding outcomes is not completely clear. Arora et al. (198) and Kessler et al. (199), in research on factors that affect breastfeeding and bottle-feeding, found that support from the mother's husband/ partner and mother (grandmother of the infant) or other family members helped to encourage breastfeeding. A mother's partner's preference for bottle or breastfeeding was particularly influential for the mother.

Rempel et al. (200) found that the fathers' perception of support for breastfeeding predicted breastfeeding success and satisfaction for men and women but also appeared to be associated with shorter breastfeeding duration. This study raised questions about the type of behavior from fathers that mothers considered to be most supportive.

Most of the mothers who participated in the interviews said that their husbands or partners weren't strong advocates of breastfeeding. While a third of the mothers said their husbands were somewhat supportive, only two said that their husbands were strongly supportive. Four mothers said that even though their partners expressed support for breastfeeding, the fathers often wanted to feed the baby formula and encouraged mothers to do the same. One mother, who was in her twenties and was breastfeeding her first child, felt that her husband, encouraging formula feeding, undermined her efforts to breastfeed and made her feel isolated because of her choices. She stated that:

> "My husband didn't understand . . . he (said), 'Why don't you just give her formula?' All he saw was the doctor saying, 'You should give her formula and that it's fine.' So that was really stressful; it caused a bit of tension between us, made me feel pretty alone, having to fight my partner on this."

Many of the mothers lacked role models for breastfeeding within their families. A third said that their mothers or sisters had breastfed to a varying degree while three mothers said that their mothers bottle-fed, with one mother stating that her mother had never wanted to try breastfeeding. Mothers also experienced varying levels of support for breastfeeding from family members. Among those who commented on this issue, the majority received limited or rather ambivalent support. Four mothers said that they received support for breastfeeding from a sister, mother or a mother-in-law.

Some mothers who did receive breastfeeding support from family members found this support, although well-meaning, sometimes increased pressure on them. One mother in her thirties who also had a toddler talked about the pressure she felt, even from those who supported her:

> "My mum was very pro-breastfeeding and I remember when I couldn't breastfeed, it was really hard because, every day, my mum would call and give suggestions on what I could do to breastfeed."

4.6.3. Mothers' Intention to Breastfeed and Expectations

All of the mothers intended to breastfeed before their babies were born. Only one mother said she was concerned that she might not be able to because of previous breast surgery. Most stressed that they wanted to breastfeed because of the nutritional benefits of breastmilk. One mother in her thirties with no previous children reflected this commitment to breastfeeding her baby because of these nutritional benefits:

> "I really, really wanted to exclusively breastfeed. Every mum wants the best for their child and then they're told this is the perfect nutrition. Formula is good but look at the checklist of nutrients and how the benefits of formula are a few lines long and then the benefits of breastmilk are pages long, . . . every drop is like liquid gold."

Almost half of the mothers said that they expected breastfeeding to be relatively easy. Several commented that they had an idealized or even fantasy picture of what breastfeeding would be like. Another mother in her thirties with no previous children described her initial view as somewhat naïve:

> "I have really high expectations of myself and being a mother and providing for my daughter. I had an ideal picture in my head that I would just be this wonderful breastfeeding mother and that it would be amazing."

The combination of mothers strongly wanting to breastfeed because of its benefits for babies and feeling that breastfeeding would be relatively easy led to feelings of distress and disappointment when problems arose. These mothers often felt isolated because they thought they were unique in facing these difficulties. One first-time mother in her thirties, who had no other children of her own, said that she thought breastfeeding would be "a breeze." She spoke of her sense of isolation when

she started facing challenges saying that: “I just didn’t expect that it was going to be as difficult as it was or that I would have any issues because no one I know had any issues.” Some mothers said that they felt that the pressure to breastfeed also arose from society.

4.6.4 Sources of Information about Breastfeeding Used by Mothers

Prior to giving birth, the majority of the mothers said that they did not receive specific instructions about breastfeeding. Four mothers had met with a lactation consultant or attended courses on breastfeeding and two said that they had attended prenatal classes which had a small breastfeeding component.

Several of the mothers said they would have liked more information about the difficulties they might encounter during breastfeeding. One mother, who was in her late thirties when she had her first baby, attended two breastfeeding classes before the birth. She said that the information she received did not fully equip her for the challenges she eventually faced. She also felt that she needed more basic information about the needs of babies in the period immediately after birth:

> “I was taught things like ‘feed off one side at a time’ or ‘offer one (breast) so baby can finish’ but there was not the education about what are common challenges with breastfeeding. I wasn’t aware that a newborn should be eating every three hours – that their tummy is the size of a pea . . . and that jaundice is extremely common . . . and that makes them sleepy.”

Online sites were the most frequent source of support and information for the majority of mothers while they were breastfeeding. A third of the mothers were connected to Facebook groups for mothers on domperidone or for those who were pumping milk. The second most popular online source was Dr. Jack Newman’s website (201) visited by five of the mothers. Other internet supports including Google Search were used by several women to research low milk supply and domperidone although the use of these resources was not explored in detail.

Half of the mothers attended breastfeeding support groups, offered mainly by public health units. A few mothers attended La Leche League from time to time. Many of these mothers said that it was difficult to attend these support groups regularly**.**

4.6.5 Mothers’ Pregnancy and Birth

Pregnancy and birth experiences can have an impact on the early establishment of breastfeeding. The majority of the mothers reported having healthy and uneventful pregnancies described in phrases like, “easy”, “healthy”, “active” or “awesome.” Three mothers described medical conditions that affected them during pregnancy including preterm labour that led to hospitalizations; three other mothers described their pregnancies as worrisome – because of issues like previous miscarriages or health issues. None of the mothers gave birth to preterm infants.

Most of the mothers (10/18) described the birth of their babies as unproblematic, however, five described interventions including two women who had Caesarean-sections, two with forceps deliveries and one who was induced. One mother said she had a third-degree tear; one woman described a very long labour. The vast majority of babies (15/18) were healthy with no problems at birth; one baby had a disability which was known prior to the birth and two had other health problems after birth that were relatively minor. Thirteen (13) mothers described themselves as healthy and without problems after the birth of their babies; three said they felt stressed or numb, and two had medical issues – one related to a significant tear and another experienced the effects of an existing medical condition for a short period of time.

4.6.6. Early Breastfeeding Challenges

A mother having skin-to-skin contact with her newborn very soon after birth is associated with breastfeeding success. The majority of the mothers had immediate skin-to-skin contact with their babies and were able to put them to the breast right away, a third said contact with their infants was delayed by one or two hours.

Most of the mothers described early problems which they felt had affected their early establishment of breastfeeding. Seven of the mothers said that a major problem they faced in the early hours and days of breastfeeding was their infants falling asleep and/or not being interested in the breast. One mother in her thirties with two other children reported her baby's disinterest made her feel very anxious,

> " . . . when I got home, trying to nurse a little more because he was losing weight so rapidly. He didn't seem to know what he was supposed to do . . . he didn't seem to be interested enough to put (in) any effort. I was incredibly worried – couldn't figure out how to get him to nurse harder."

Ten of the mothers reported their infants developed jaundice, either in the hospital or when they returned home. Several of the mothers, whose babies developed jaundice when they were in the hospital, were placed under bilirubin lights. These mothers felt that this interfered with the early establishment of breastfeeding because they were unable to hold their babies frequently or feed them on demand.

Just under half of the mothers reported problems with their babies latching on to the breast correctly which initially made breastfeeding difficult. For all but one mother these problems were resolved early in the postpartum period. Three mothers felt that tongue-tie was affecting the latch and that delays in fixing it affected successful breastfeeding and increased their distress. As stated by a first-time mother in her thirties who initially had no problems with breastfeeding but soon felt that her baby was not regaining her birth weight:

> "It became very clear to me that my supply was completely insufficient due to, probably poor latching. And [the lactation consultant] said that the baby had a tongue and lip-tie and a high palette and a recessed chin and I had flat nipples. [It was] like major anatomy incompatibility. I was feeling very despondent and very upset. I was devastated that my body couldn't feed my baby."

All of these breastfeeding challenges, many of them normal for many new mothers, led to mothers feeling anxious and concerned about their babies being able to breastfeed effectively.

4.6.7 Institutional Policies Affecting Breastfeeding

All the mothers except one gave birth in hospital. Over half of the mothers who gave birth in hospital were discharged in 24 hours or less; a third of the mothers stayed from 2 – 5 days and one mother whose child had an anticipated disability stayed longer.

Early discharge for mothers meant that breastfeeding had not been established at the time of leaving the hospital and jaundice, a condition experienced by many babies after birth, had not fully developed. For three mothers, jaundice became worse after discharge and in one of these cases the jaundice led to the baby and her mother being readmitted to hospital.

4.6.8 Non-Pharmacologic Methods Used by Mothers to Increase Milk Supply

The use of non-pharmacologic remedies to try to increase milk supply was common among over half of the mothers. These mothers tried from one to nine different non-pharmacologic galactogogues. The most common substances were fenugreek, milk thistle and specialized teas. None of the mothers who used these remedies assessed them as having a significant effect on their milk production.

In retrospect, some of the mothers perceived their use of these products as burdensome and felt that they reflected a desperate need for them to "try anything" that might produce more milk. One mother in her early thirties with no previous children described her extensive use of these products and her attitude towards using them:

> "I was willing to try anything. I tried nine different herbal supplements to help with milk production. I ended up ordering anything I could find online. I tried all the teas that were in the stores; I tried the cookies, I tried the . . . Gatorade, drinking coconut water . . . coconut milk. I tried the oatmeal, like big pots of oatmeal . . . and eating, like, five cups of oatmeal a day."

A third of the mothers did not try any of these remedies, some saying they were unscientific or hadn't worked when they had tried them when breastfeeding their other children. The most common non-pharmacologic intervention introduced to mothers as a way of addressing LMS was supplementation with formula. The vast majority (15/18) of the mothers were advised to use formula to help feed babies and, for most, this supplementation was recommended by healthcare providers very soon after the baby's birth. About a quarter of the mothers were advised to start using formula

within the first 1 – 2 days after their baby's birth, a third were advised to start using formula 3 – 7 days after birth and the rest of the mothers started using formula in the second week postpartum.

Formula was recommended by all types of health care providers including hospital and public health nurses, lactation consultants and midwives. Most of the mothers were advised to use formula during the period when their milk supply was just being established. The use of formula by mothers led to the introduction of demanding pumping and feeding schedules where mothers had to pump, feed their babies on the breast, then on the bottle with pumped milk and then to "top up" with formula. Many mothers described this schedule as overwhelming, stressful and exhausting.

Three mothers were given nipple shields as a method for improving milk supply. One mother in her late twenties with no previous children later saw this as an "easy fix at the hospital", but one that had long-term negative outcomes for her and her baby which she considered to be unnecessary and stressful:

> "I think it was an easy fix for them [hospital] to hand me a nipple shield and then the baby will latch because it's a giant plastic nipple like a bottle . . . it took something away from me. I can't get him to stop (nursing) without the nipple shield . . . there's almost no turning back . . . big inconvenience because anytime I want to nurse when I am out somewhere, I have this silly thing with me."

4.6.9 The Role and Impact of Healthcare Providers on Breastfeeding

During the early postpartum period, most of the mothers had substantive contacts with two to nine different healthcare providers in hospital or after they left the hospital to assist them with breastfeeding. The vast majority of mothers had contact with physicians and at least half said they received breastfeeding support and information from hospital nurses, midwives and public health nurses who worked in the community. Two-thirds of the mothers received help from lactation consultants, most of whom were paid privately. Mothers were highly involved with these healthcare providers and stressed the importance of having breastfeeding experts to consult particularly because some commented that their physicians were not readily available. In addition, over half the mothers were discharged from the hospital within one day. This meant that their milk supply was not established and babies were still losing weight, a normal part of the early postpartum period, but worrying for many mothers. Many of the mothers were also dealing with their babies having symptoms of jaundice which they felt exhausted their babies and reduced their alertness and interest in nursing.

The majority of the mothers found that the support they received from most healthcare providers was helpful. One mother in her mid-thirties with her first child stressed the practical help she received just after her baby was born:

> "The [hospital] nurses . . . were really awesome. It was really hard . . . in the middle of the night when all he wanted to do was nurse, and I really wanted to sleep . . . the nurses [helped me] with my hold . . . there was also the lactation consultant who I saw a couple of different times, who got me set up with the pump."

Another mother in her late thirties and with no previous children also acknowledged receiving good care from healthcare providers. However, she expressed concern about a lack of continuity of care which affected her breastfeeding experience and which she felt had contributed to her problems with milk supply and to her use of domperidone.

> "I would say, overall, I got really great care. I think everyone was really well-meaning. I don't know how to describe it; . . . there's no continuity in the care; so, . . . I think domperidone is prescribed very casually . . . without anyone actually following up, going, 'Is this helping? Do you need to be taking more? Do you need to be going off it now?' I just felt like it was prescribed and then I was kind of on my own."

Three other themes were identified by some of the mothers in their interactions with healthcare providers that negatively affected their confidence and experience with breastfeeding, increased their worries about their milk supply and that may have contributed to their eventual use of domperidone. These themes were:

- the frequency with which mothers received contradictory advice from different healthcare providers and the negative impact this had on their confidence;
- worrisome statements about LMS made by some healthcare providers which led to some mothers experiencing more stress and believing that LMS was a permanent condition;
- the impact of demanding pumping and feeding schedules resulting from the early introduction of formula. Many of the mothers felt these schedules were overwhelming and exhausting when they were still recovering from the birth of their babies.

The majority of mothers reported being given contradictory advice from some healthcare providers about breastfeeding techniques and about LMS and the best ways to treat it. Sometimes conflicting advice was given by healthcare providers on the same hospital staff or from different midwives in the same practice. This occurred with all types of healthcare providers including physicians (although they were least involved), midwives, lactation consultants, hospital and public health nurses. Contradictory advice left mothers feeling confused, exhausted and not knowing what to do. For example, one mother in her late thirties, with a baby under six months old and no previous children, described how this conflicting advice confused and frustrated her, for example:

> "There was a feed where my daughter had 6 ounces of formula after I breastfed her, [recommended by a nurse] and then I was told [by another healthcare provider] that she was way too young to need to eat that much. And then the lactation consultant basically just told me that my whole feeding plan was all wrong. I should be feeding her less, and more frequently rather than feeding her as much as she wants at any given feed. She gave me this notebook to start tracking every little last detail, and it just made me so stressed out . . . . And then when I went and saw the other consultant, her advice was completely different."

Another mother, who also had a previous child she had breastfed, said she got "every part of the spectrum of information" from healthcare providers including advice to pump every two or three hours or not to stress and pump every four hours or to nurse her baby whenever he wants.

About a third of the mothers identified pivotal comments from healthcare providers that left them feeling that their problems with milk supply were endangering their babies. Some mothers were also told that LMS was a permanent condition. Several were told that there was something wrong with their breasts and that they might never be able to breastfeed; one was told in the first few days postpartum that she was probably "just one of those people who can't produce enough milk" even though her milk supply was still being established.

Some of these comments appeared to reflect a misunderstanding, on the part of some healthcare providers, of the lactation process or of the supportive environment mothers need in order to establish breastfeeding. For example, one mother was told less than 24 hours after the birth of her baby that she should be "spraying milk by now." Another nurse told her in the first few days postpartum that she had four hours to produce enough milk before an intervention would take place. This made her anxious about nursing and did not help her milk production.

When one mother in her twenties with no previous children attended a breastfeeding clinic for help, she was asked to identify her breastfeeding goals to a lactation consultant and, in response, she said that she wanted to,

> " . . . exclusively breastfeed, [with] no formula. I made that extremely clear. If I needed to pump around the clock for the next few months, that was what I was willing to do. She looked at my breast and said, 'We're going to help you, but you'll never make enough milk for your baby' . . . and she came back with a bottle of formula."

This mother ended up finding other help with breastfeeding and in a few months was able to exclusively breastfeed without supplementation.

For some mothers, these types of comments ignited fears that their situation was hopeless and that they were possibly to blame for not having enough milk. One mother in her thirties, with a baby under three months old, described her struggle to produce sufficient milk after many attempts:

> "I was so emotional because I really wanted to breastfeed him. And when the milk hadn't come in at the week/week and a half mark, I started to kind of think it wasn't ever going to happen, which was upsetting for me. I had a lot of mom guilt, whatever you'd call it."

Fifteen of the 18 mothers were advised to use formula within the first few days or weeks postpartum. Formula introduction was usually coupled with recommendations for mothers to frequently pump milk and to bottle and formula feed. Several mothers felt overwhelmed by the demands of pumping and supplementing when they were already deprived of sleep. One first-time mother in her early thirties described the feeding process she was advised to do as increasing her sense of failure and contributing to her exhaustion and depression:

> "[I was] . . . essentially only sleeping in hour chunks at that because the feeding process would take an hour because there's breastfeeding and then the formula and then the pumping. And then I had to wake her up in another hour . . . , because it was two hours from start-of-feed to the start of the next feed . . . so that whole process that they had me do, I think very much, was a trigger to some really, really serious postpartum depression."

4.6.10. Approaches Used to Diagnose LMS

Section 2.4.2 discussed the methods that are most commonly used to identify and diagnose LMS. The most validated method involved multiple baby test/retest weighing before and after breastfeeding during a twenty-four-hour period (79, 80).

Normal lactogenesis involves a period of weight loss by babies after birth and variations in the amount and time this weight is regained in the first few weeks postpartum. It is well established that weight gain is slower among babies who are exclusively breastfed than among babies using formula. In addition, there are individual variations among babies.

Mothers were asked to identify how LMS was determined in each of their cases. An understanding of when and how LMS is diagnosed is important because once LMS is identified, it can lead to many other interventions such as the introduction of formula, extensive pumping schedules and the prescribing of domperidone. Results indicated that the approaches used to diagnose LMS often lacked a clear evidence base and a consistent approach. Diagnosing a mother with LMS within the first few days postpartum, when her milk supply was still being established, was relatively common. Qualitative assessments of the baby's behaviour by the mother or healthcare provider were considered to be indicators of LMS even though these methods, when considered on their own, may not be completely reliable. Two mothers had no assessments at all; they simply assumed they would have milk supply problems because they had had them with a previous infant.

Only two women had test/retest weighing of their babies after feedings but in both cases, these consisted of one test within a 24-hour period. One mother was asked by her public health unit to go for a test/retest weighing of her baby every other day for six weeks when her baby was assessed as not gaining sufficient weight at two weeks of age. This first-time mother in her early thirties

described these testing procedures as distressing and eventually asked them to be discontinued because they were not taking into account her baby's over-all needs. She described them as being,

> "[It was] stressful for me because in the waiting room and they strip down your baby . . . a 2-week-old baby naked is not a happy camper, then you quickly wrap them up, and then you feed them; they did the weighing before and after feeding so they gauge what she was ingesting. But it was not just one or two times I was there; I was there almost, like, every other day for [4] weeks. And finally, I said that 'I can't do this anymore. It's driving me crazy.' Because I think . . . they were weighing her every day instead of looking at the bigger picture from between 2 weeks and 6 weeks."

Half of the mothers were told they had LMS when their babies had not regained their birthweight within the first 2 – 4 days after birth.

Three of the mothers interpreted certain aspects of their baby's behaviour (fussiness and frequently waking up at night for feeding) as indicating hunger rather than normal early infant behaviour. This contributed to their belief that they did not have sufficient milk to satisfy their babies. These mothers were advised to use domperidone to increase their milk supply and to supplement with formula. Two of these mothers said that formula helped their babies sleep better.

In another case, a healthcare provider identified signs of dehydration in the baby at three days postpartum which was determined to be caused by LMS. In another case, a baby's weight gain slowed at two months and this was interpreted as LMS. The milk supply of this mother had been adequate up to this point and the mother's report of her baby having had a recent virus she felt was a factor in this weight loss was not taken into account.

4.6.11 Mothers' Prior Knowledge of Domperidone

Almost half of the mothers said that they knew nothing about domperidone before it was prescribed. Just over a third knew a bit about the drug through their own research. The vast majority of mothers did not recall hearing about the potential cardiac risks of domperidone from healthcare providers who prescribed or recommended it. Three of the mothers said that their physicians told them domperidone carried cardiac risks but that these risks only applied to elderly women.

4.6.12 Mothers' Experiences with Testing before Domperidone Prescribed

It is recommended that clinicians undertake three types of assessments before domperidone is prescribed. These include taking a patient's personal and family history with a focus on assessing cardiac-related risks, a review of whether a patient is taking other QT-prolonging drugs that might elevate the risk of taking domperidone and, in some cases, ordering an ECG if potential patient cardiac risks have been identified. The interview asked mothers what assessments were undertaken by their healthcare providers prior to their prescribing domperidone.

More than half of the mothers said that none of these three types of assessments were undertaken by their healthcare provider prior to domperidone being prescribed. Under a third of the

mothers said a general medical history was taken but only two mothers were asked about other medications they were using. One mother said she received an ECG but said this was because she was taking a very high dose of the drug (160 mg/day). Another mother said she had had heart arrhythmia problems during pregnancy and had worn a Holter monitor to track her heart rhythms at that time but that no further cardiac function tests were undertaken before she was prescribed domperidone.

4.6.13 Domperidone Use Patterns

Just under a third of the mothers were prescribed domperidone within a week of their baby's birth or before birth in the case of two mothers who had used it with previous babies and expected they would have LMS again. About half of the mothers received a prescription when their babies were 1 – 2 weeks old and the rest of the mothers were prescribed the drug when their babies were more than two weeks old.

In terms of duration of use, almost half of the mothers who were interviewed were still using domperidone to treat LMS at the time of the research interview. This time ranged from eight weeks to ten months. Among the mothers who had already stopped using domperidone, over half had stopped using the drug within three months and three mothers had used the drug for over three months.

Health Canada and the European Medicines Agency (127,124) have recommended a maximum dose of 30 mg/day as the safest dose of domperidone. The EMA advisory did not specify that their dose recommendations applied to the use of domperidone to treat LMS – this is not a common use in Europe. The 2015 safety advisory from Health Canada, described the advisory (including dose recommendations) as being directed to all patients using domperidone whatever the condition being tested. However, the use of domperidone to treat LMS was not specifically mentioned as being one of these conditions.

Only three of the 18 mothers were prescribed domperidone at or below 30 mg/day. Half of the mothers were prescribed 80 mg/day or more. A few of these mothers were taking 90 – 160 mg/day, three or four times more than the dose levels advised by Health Canada.

Just under a third of the mothers who received doses over the recommended guidelines said that they were influenced by the domperidone dose levels sometimes recommended by key influencers such as Dr. Jack Newman, a breastfeeding advisor who runs a breastfeeding support website and Facebook page (173, 202). In some of his materials he suggests that breastfeeding mothers with milk supply problems start with 30 mg/day and then increase the dose to 60 mg/day and then up to levels of 120 mg/day, if needed.

Some of the mothers strongly believed that 30 mg/day was ineffective and that higher doses were necessary to increase milk supply. In several cases, mothers increased the doses recommended by healthcare providers by taking more than was recommended – a form of self-

medication. In two of these cases, the mothers persuaded their own healthcare provider to override the concerns of pharmacists who were dispensing the drug. One first-time mother in her twenties, who had received an ECG, described the difficulties she experienced getting the dose of 90 mg/day she felt was necessary from her healthcare provider and that was sometimes recommended by Dr. Jack Newman who she considered an expert on the use of domperidone to treat LMS:

> "And then she gave me the prescription for domperidone and I go to the pharmacy and they refuse to fill out because they said, 'Ninety milligrams is too high a dose, you're going to have a heart attack and die.' I paged my midwife because I need this medication. So, she talked to them and made them give it to me. Every time I go to fill it, I fight with the pharmacist."

This mother believed that pharmacists need more education on LMS and should be made aware of Dr. Newman's information on dose levels for domperidone.

In the case of another mother, when her pharmacist expressed a concern about filling her prescription of 80 mg/day, she doubled up on the smaller doses she received in order to reach the higher dose level she believed was most effective. These results indicate that, among many of the mothers, there was the belief that doses around 30 mg/day are ineffective for increasing the milk supply and that, for some, they are willing to self-medicate in order to get the dose levels they feel they need. Several other mothers mentioned that, although they were told of potential cardiac risks by their healthcare providers, these risks were described as only being applicable to elderly women.

4.6.14 Adverse Effects of Domperidone Identified by Mothers

Mothers were asked to identify any adverse drug effects of domperidone that they felt had affected their babies or themselves. None of the mothers identified any adverse effects of domperidone on their babies. However, more than half of the mothers identified a range of ADRs that they attributed to domperidone.

The most common ADR identified by the mothers was unexpected weight gain. Half of the mothers with ADRs said they felt domperidone had contributed to weight gain that didn't seem to relate to how much they were eating. The second most commonly identified ADR was digestive problems that consisted of gas pains, nausea and loose bowels. Three mothers said they experienced headaches when taking domperidone; these were described by mothers as sometimes severe or continuous.

Two mothers said they experienced disturbing psychiatric symptoms when they tried to reduce or stop their use of domperidone. These symptoms appeared to mimic withdrawal symptoms that are commonly associated with withdrawal from neuroleptics and included increased anxiety, dysphoria, and akathisia. Domperidone is in the family of neuroleptic drugs and several case studies have identified these effects (139, 140). One mother who experienced these reactions described the devastating impact of these types of psychiatric symptoms:

> "I felt like my life was over, everything was terrible. And it made me feel like that, where you can't be inside, you can't be outside, you can't be sitting down, you can't be laying down . . . you can't even be in your own skin; everything just feels awful. It came on fairly quickly, within a matter of days. And I wouldn't say that it's gone."

4.6.15 Mothers' Views of the Effectiveness of Domperidone

Only a third of the mothers felt that domperidone had been effective in increasing their milk supply. Two of these mothers felt that very high doses were needed to produce this effect. For these mothers, domperidone was seen as being largely responsible for helping them to breastfeed – some with supplementation by formula and some without. One mother in her early thirties with two other children and who had used domperidone with all of her babies felt that it had made breastfeeding possible:

> "I was quite thankful to start taking domperidone and to be able to breastfeed him till he was 19 1/2 months [old]. I don't think that I would have been able to have enough supply to be able to breastfeed my children. And I think they would have then been formula-fed babies. None of them have had formula. It's basically just been breastfeeding."

A majority of mothers were either uncertain about whether domperidone worked or felt it had not been effective at increasing their milk supply. About half of the mothers said that they were uncertain or ambivalent about whether domperidone had helped them, some stating that other factors such as increased pumping could have been responsible for increasing their milk supply. The comments of one first-time mother in her late thirties who was still taking domperidone reflected this uncertainty about the effectiveness of the drug. She, along with some other mothers, also questioned whether her milk supply had increased because of other things she had done, saying that:

> "I'm not convinced that this domperidone is helping. I take it because I want to feed my son and a doctor prescribed it to me. But I don't know . . . if it was the drug that helped me, or did I just start to get more sleep and start to relax more . . . eat better and got more on a cycle, and therefore whether [it was] the pill that helped."

Another mother said that later she wondered if domperidone had really contributed to her milk supply, saying that "I want to say that it did but I almost felt it was like a placebo for me." Three of the mothers said that they believed domperidone had no effect on their milk supply.

4.6.16 Mothers' Knowledge and Response to Domperidone's Off-label Status

Prescribing domperidone to treat LMS is an off-label use that has not been approved by Health Canada. When a drug is prescribed off-label it may not have undergone the testing, including clinical trials that drugs undergo in order to be approved. Research suggests that both healthcare providers and the public lack information on whether a drug is approved or unapproved for a specific indication (22, 48, 49).

Mothers were asked whether they were aware that using domperidone to treat LMS is an off-label use and what, if any concerns, they might have about being prescribed a drug off-label to treat

LMS. Two-thirds of the mothers said that they were aware that the prescribing of domperidone to treat LMS was an off-label use. In many cases, mothers had researched the drug themselves or had read a pamphlet about domperidone that was provided by public health. A third of the mothers said that they were not aware that using domperidone to increase milk supply was an off-label use.

Over half of the mothers said they had no problem using a drug that was being prescribed off-label, primarily because they trusted the decisions of their prescribers. As one first-time mother in her late thirties said, "I've trusted that the medical profession has done their research, that there's no negative or serious, negative consequences to using a drug in that matter when it's not technically what it was originally created for." Several of these mothers also said that if a drug was effective for a specific condition, despite it being prescribed off-label, it should be available for those who needed it.

Though generally comfortable with its use, a third of the mothers said that it was important that more research on domperidone's effectiveness and safety be done. One first-time mother in her early thirties reflected concerns about the lack of research on the off-label use of domperidone. Her comments reflected the importance of understanding the potential risks of a drug as fully as possible:

> "I think that [OLU] is okay. But it does make me worry a little bit there hasn't been enough research done on it, and that maybe all the effects aren't fully known. Because, if lactation was just kind of a surprise benefit, you don't really know what else maybe it could be doing that won't show up until long-term use years down the road."

4.6.17 Other Factors Influencing the Mothers' Experiences with LMS

Mothers were asked whether any other beliefs, attitudes or broader socio-cultural factors had affected their experiences with breastfeeding or with LMS. The main theme that emerged was that a third of the mothers felt there were strong social pressures to breastfeed and that there was a stigma against using formula or adopting a more flexible approach to feeding their infants. Some mothers talked about feeling embarrassed about having issues like LMS, particularly if peers or family members appeared to have had no problems with breastfeeding. One first-time mother in her late thirties described her shame at having to use formula to address her problems with milk supply when all her family members had breastfed:

> "Everybody [in the family] breastfed, . . . I was embarrassed that I couldn't produce enough . . . but I hid the fact that I was supplementing with formula that first little bit. I would go into the backroom and sneakily make a formula for my daughter . . . and then come back and pretend that I'd just finished nursing her."

Another mother commented that, "even going to the grocery store to get formula . . . I am embarrassed to be buying it." However, one mother said the pressure to breastfeed did not come from external sources but came mainly from herself.

Several mothers felt that a societal bias towards breastfeeding made it more difficult to handle the challenges they experienced. These mothers commented that that they had underestimated how difficult breastfeeding would be. However, several mothers said that social support for breastfeeding

validated their belief that the challenges they faced were worth it. As stated by one first-time mother in her early thirties who faced many challenges in order to establish her milk supply:

> "Most people do think it's obviously the best to breastfeed rather than to give formula . . . I think that's what's made this struggle/journey worthwhile for me . . . I think the easy way out would have just . . . to have been . . . to say, 'Oh, you know, I'll just hand him a bottle of formula and job done,' and I would have had a lot more sleep and a lot more . . . sanity, especially in the beginning. But I think just society's views and my own family and my own opinions on it is that, it's a struggle that's worth doing."

Other factors that influenced individual mothers' experiences of breastfeeding and a decision to use domperidone included having to go back to work, feeling that the previous use of domperidone meant it needed to be used with subsequent babies and the high costs of using formula when it was recommended. Some mothers also said breastfeeding was affected by their difficulties interpreting whether their babies were satisfied after a feeding. Their lack of experience with breastfeeding was exacerbated by the lack of social modelling of breastfeeding.

Several mothers identified family-related factors affecting their breastfeeding experiences. In one case, a mother had two other children to take care of when breastfeeding her third baby. Another said that her family's acceptance of any feeding choice she made helped her make the best decision for her.

4.6.18 Gaps in Breastfeeding Support Services

Over half of the mothers identified gaps in breastfeeding services that that they felt would have been helpful. Most of their comments focused on information that they felt would have helped them face challenges. One first-time mother in her early thirties felt she learned a lot from healthcare providers about the benefits of breastfeeding but they did not "necessarily talk about a [baby] not getting enough fluids [and] what problems that could have."

One of the mothers felt that she lacked information on the possible safety concerns of domperidone when taken at high doses. Another first-time mother said that she would have liked more information about the effective latching of the baby at the breast which affected her ability to breastfeed:

> "In the hospital, they did a really good job; they make you watch a video before you're released. They do a good job of teaching that you obviously have to eat more healthy calories and watch what you eat and drink a lot of water. But they don't talk a lot about issues that you may come up with; they . . . go over the basics for if you have an ideal experience. I have flat nipples; the baby has almost no chance of latching on those without some real help from a lactation consultant."

One mother in her early thirties who had two other children and used domperidone while breastfeeding each of them spoke about the diminishing lack of services she had observed at her local community-based health unit saying that:

> "It's harder to get support at our local Health Unit. I had asked if there was a lactation consultant I could see, and they had said that their lactation consultant didn't really do what they call frontline work. She was there mostly for paperwork, and that they weren't doing all of these breastfeeding drop-in clinics anymore. They don't have a comfortable place that you can nurse your child in the room, whereas they used to have actual rocking chairs in the room. It's a lot more difficult to get breastfeeding support locally now than it was with my previous child."

Without community-based, publicly funded support, the alternative for mothers is hiring a private lactation consultant, at a cost of about $100/hour, which was out of reach for many of the mothers. One first-time mother in her early thirties spoke about the quality of breastfeeding support she felt was lacking. She had had many early breastfeeding challenges including problems with effective latching, exhaustion, sore and cracked nipples and feeling her baby might not be getting enough milk. Looking back, she said:

> "I felt like I needed someone who was a little more kind and . . . slow, patient and supportive . . . to come to sit with me, to watch what we were doing, spend time, and to, help me, as opposed to just . . . dumping their information on me and then leave . . . . If I had more information and better support, I could have avoided that whole . . . rigmarole [diagnosis of LMS]."

Many of the mothers spoke about how breastfeeding is often seen as an idealized experience and that normal challenges, experienced by many mothers with new babies, are downplayed or not discussed. This led to some of the mothers blaming themselves and feeling like they were failures if they faced difficulties. Some of the mothers later saw that their idealization of the breastfeeding experience was unrealistic and impossible for most mothers to attain. One mother summed up some of these sentiments by saying, "I think [if you're] more the super-mom . . . the excellent mom that can breastfeed, has a natural birth . . . and is able to stay at home, I think you're like the magical unicorn." This mother put into words the conflict between an idealized view of both childbirth and breastfeeding and the impacts on women who felt that they haven't been able to attain it.

4.7 Summary of Key Results from the Mothers' Interviews

Eighteen mothers who had used domperidone within the first six months of their baby's birth participated in the interviews. Most of the women were first-time mothers. Among the four mothers who had other children, three had previously used domperidone. Although all the mothers were deeply committed to breastfeeding only a third had mothers who had themselves breastfed. Only a third described their partners as being supportive of breastfeeding, only two said they were strongly supportive. Some said that they felt that that their partners encouraged formula feeding. Almost half of the mothers said that they expected breastfeeding to be relatively easy. The combination of a strong commitment to breastfeed and being unprepared for challenges led to feelings of distress or personal failure among some women when problems they didn't anticipate arose.

Prior to giving birth, most of the mothers did not access specific information about breastfeeding. Four mothers received some information, primarily through pre-natal classes. Online sites such as specialized Facebook groups were used by the majority of mothers after their babies were born. Jack Newman's site on breastfeeding was the second most popular online resource that was mentioned by the mothers. Half of the mothers attended drop-in breastfeeding support and information groups but some said they found support groups like La Leche League difficult to attend.

All of the babies were full-term babies. Two babies were delivered by caesarian-section and one was a home birth. Just over half of the women were discharged from hospital in 24 hours or less. This meant that many mothers left the hospital when breastfeeding had not been clearly established and issues like infant jaundice had not fully appeared. For some mothers, the transition from the hospital to the community also led to problems in the continuity of care.

In hospital two-thirds of the mothers had early skin-to-skin contact with their babies; for a third of the mothers this contact was delayed. Two of the main challenges faced by at least half of the mothers and infants in the early postpartum period were infants having jaundice and, for some mothers, having difficulty latching the baby to the breast for effective nursing.

Just over half of the mothers used a variety of non-prescription galactogogues such as fenugreek and milk thistle to increase their milk supply. However, none of the mothers assessed these remedies as having significant effects. Looking back, many of the women perceived the use of these products as being a burden and reflecting their need to "try anything" to increase their milk supply.

All but three of the mothers were advised to use formula within the first few days or weeks of their baby's birth. The recommendation to incorporate formula into feeding schedules often led to complicated daily pumping, bottle and breast-feeding regimens which some mothers found overwhelming, stressful and exhausting.

Most of the mothers had contacts with a significant number of different healthcare providers who provided information and support around breastfeeding at the hospital or in the early postpartum

period at home. Half received help from midwives or hospital-based nurses or those working in public health centres. The most commonly accessed health professional, by two-thirds of the mothers, were lactation consultants, often paid privately.

Relationships with healthcare providers were crucial for the mothers and were often seen as helpful but were sometimes problematic. The majority of the mothers felt that they received contradictory advice about building their milk supply. One mother felt this was due to the lack of continuity of care and the fragmentation of services. Another concern, expressed by a third of the mothers, was when healthcare providers made comments about their inability to produce milk that scared them and made them feel they were jeopardizing the well-being of their babies. In some cases, these comments were made only 1 – 2 days after birth, prior to a mother's milk supply being established.

Most of the methods used to determine whether mothers had LMS and whether domperidone should be used were qualitative, inconsistent and lacked an evidence base. Only three mothers had test/retest weighing of their babies but, in all of these cases, there was no more than one weighing in a 24-hour period. In half of the cases, mothers were told they had a problem with their milk supply when their babies were not gaining weight, even when they were only a few days old.

Just under a third of the mothers received a prescription for domperidone in the first week after their baby's birth or even before their babies were born (two mothers who had had problems with milk supply with previous babies and thought it would be needed again). Half received their first prescription when their babies were 1 – 2 weeks old.

Despite recommendations for specific medical assessments to be undertaken prior to a patient being prescribed domperidone, for more than half the mothers there were no specific medical assessments carried out by a healthcare provider before the drug was prescribed. For those who did have some kind of assessment, just under a third said a medical history was taken, but only two mothers were asked about the other medications they were taking. One mother said she had received an ECG but this was because of the high dose (160 mg/day) she had been prescribed. Most women were not informed about the potential cardiac risks of the drug by their healthcare providers.

Only three mothers were prescribed the dose of domperidone (30 mg/day) recommended by Health Canada and the European Medicines Agency. Half of the mothers received 80 mg/day or more; in some cases, doses were as high as 90 – 120 mg/day. Dr. Jack Newman is a physician who provides breastfeeding information and support through a website and Facebook page. He is a published author and a co-author of papers which provide support to breastfeeding mothers who have problems such as poor latch or LMS (126, 203) He has advocated the use of domperidone starting at 30 mg and going up to 120 mg/day, if required. A third of the mothers said that information from Dr. Newman influenced their decision to use domperidone and to ask for higher doses. The results of

the interviews suggested that some mothers believe that doses at 30 mg/day are not effective at increasing a mother's milk supply.

Mothers did not identify any adverse effects of domperidone related to their babies while they were using it for breastfeeding. However, more than half of the mothers identified ADRs related to themselves. The most common was weight gain, followed by stomach problems and headaches. Two women noted disturbing psychological symptoms when they tried to stop taking the drug. This is likely due to the fact that domperidone is in the family of neuroleptics.

Results of the interviews suggest that only a third of the mothers who had used domperidone felt that it had increased their milk supply. Most felt that domperidone had not increased their milk supply or were uncertain or ambivalent about its effects.

Research suggests that, in general, the public is unaware whether a drug is being prescribed on or off-label. However, two-thirds of the mothers knew that using domperidone to treat LMS was an unapproved use. Over two-thirds said they had no problem using a drug for an off-label indication because they trusted the decisions of their healthcare providers and felt if a drug worked it should be made available. However, a third of the mothers said that more research on the drug's safety and effectiveness probably needed to be done. Only one mother said she was concerned when she heard that using domperidone to treat LMS was an unapproved use.

The research explored whether there were other socio-cultural factors that influenced a mother's experiences with domperidone or with breastfeeding. The main theme that emerged, expressed by about a third of the mothers, was that they experienced strong social pressure to breastfeed and felt they were stigmatized if they did not. Some mothers felt embarrassed when they had trouble breastfeeding especially when other friends and family members didn't appear to have problems.

Mothers also identified gaps in information or support services which they felt would have improved their breastfeeding experiences. One concern was that, while there was support for breastfeeding, little information was available on the challenges that could occur. Several mothers said that they did not expect breastfeeding to be so hard. When problems occurred, mothers often blamed themselves and felt like failures.

Several mothers commented that local breastfeeding support, provided at community-based public health clinics, was being reduced. This resulted in some mothers having to hire the private services of lactation consultants, a service that was out of reach economically for many mothers. Mothers also experienced a lack of continuity of care when they left the hospital and returned to their homes in the community.

5.0 FINDINGS FROM THE HEALTH CANADA POLICY ANALYSIS

5.1 Questions Addressed in the Policy Analysis

The goal of my research was to examine the prescriber, patient, socio-cultural and policy factors that have contributed to the increase in off-label prescribing of domperidone to treat LMS in BC. Chapters 3.0 and 4.0 provided data on the drivers that may be contributing to domperidone use among midwives, family physicians and breastfeeding mothers. This chapter presents the results of a review of Health Canada's administrative policies and regulations to determine whether and to what degree they address off-label prescribing in general, the off-label use of domperidone, and to identify important gaps in these policies where these exist.

The policy analysis addressed three questions. Questions 1 and 2 are discussed in this section. Question 3 is discussed in Chapter 6.0 where the recommendations arising from the research are made.

1. How has Health Canada addressed off-label prescribing and the prescribing of domperidone off-label to treat LMS?
2. What, if any, policy gaps and limitations in policy exist in relation to how Health Canada is addressing off-label prescribing?
3. If limitations in Health Canada's response to off-label prescribing exist, what policy recommendations could contribute to improvements in the efficacy and safety of off-label prescribing.

This chapter includes the definition of policy used for this analysis, the key areas of policy that were reviewed, the approach used to analyze the policies and the findings from the review.

5.2 Policy Analysis: Definitions and Purpose

I am defining policy as 'a product or outcome of the political system . . . designed to make decisions about the public good and that includes institutional policies, (e.g., 'organizational guidelines, internal agency decisions or memoranda that guide organizational behaviour and functions' (202: p.2). I am using the World Health Organization's definition of health policy as the ' . . . plans and actions that are undertaken to achieve specific health care goals within a society' (203: p.2).

The policy analysis is focused on the decisions and actions undertaken by Health Canada to achieve broad objectives related to therapeutic products specified under the *Food and Drugs Act* (FDA). The mandate of the F&DA is to protect the safety of food, drug, cosmetic and medical device products used by Canadians (35).

Bill C-17, *The Protecting of Canadians from Unsafe Drugs Act* (*Vanessa's Law*) (204), amended the FDA and received Royal Assent on Nov 6, 2014. The focus of *Vanessa's Law* is on strengthening drug safety oversight, improving institutional reporting of serious ADRs and promoting

transparency within Health Canada. *Vanessa's Law* gives the Minister of Health the power to require actions by market authorization holders when there is a belief by the Minister that a drug might present a serious risk of injury to human health. The Act is named after Vanessa Young who died from cardiac arrest after taking a QT-prolonging drug which already had been identified as having safety concerns and had been withdrawn from the US market (205).

How drug safety is managed through the health policies, laws and regulations of a health regulator has broad implications for the well-being and safety of citizens. Up until the adoption of *Bill C-17*, the FDA gave only limited powers to Health Canada to respond to safety problems arising from a therapeutic product. For example, previously, the Minister of Health could revoke the Notice of Compliance for a prescription drug but could not order the drug off the shelves; this had to be done by the drug company involved. This led to long delays allowing unsafe drugs to continue to be sold. New powers allow the Minister to recall a drug or require changes to a product label.

Rodwin (206) points out that off-label prescribing undermines existing regulatory and policy mechanisms. These have been put in place to determine whether a drug is sufficiently safe and effective to qualify for market approval and sale.

Data from the policy analysis helps to 'complete the picture' of how factors at different levels in the SEM (Table 1) might contribute to off-label prescribing either at the individual level or through the interrelationships between levels. The policy and enabling environment is identified as a distinctive level in the SEM and is considered to be an overarching level that helps shape or enable individual and collective responses to a health-related behaviour such as off-label prescribing.

The policy analysis was also used to identify specific gaps in policies related to off-label prescribing as well as to recommend areas for future research and policy reforms to improve drug safety.

5.3 Sources of Information for the Policy Analysis

Four sources of information were used to define the policy areas for review and to gather information on the intent, audience and content of specific administrative policies that appeared to be relevant to off-label prescribing. These were: a search of the grey and academic literature, a review of administrative policy and policy-related documents on Health Canada's website, discussions with officials from the Marketed Health Products Directorate of Health Canada and consultation with two Canadian health policy experts.

The literature review considered literature that was generated between 1995 and 2018. This time was chosen because it covered the period in which domperidone became a generic drug, when safety concerns about the drug became more evident and resulted in Health Canada undertaking two Safety Reviews on domperidone and issuing two health warnings to the public and healthcare providers.

The academic and grey literature review involved building a key word search through OVID Medline through the use of MeSH key words and related terms, (e.g., off-label use, off-label prescribing, unapproved/unauthorized drug uses, marketing authorization), synonyms for prescription/prescribed drugs in conjunction with broad search terms such as Canada+policy+public policy. The search plan was developed with the assistance of a UBC Health Librarian. Databases searched for publications included OVID Medline, the Cochrane Library, CIHI, CADTH, Google Scholar, Grey Matters, Global, ProQuest for dissertations, Embase, and the Federal Science Library.

The most significant source of information on Health Canada's administrative policies was comprised of information available on Health Canada's website. This website includes legal and regulatory information related to prescription drugs, specific policies, guidance documents and related descriptive documents that explained components of the policies or recommendations for implementation.

In order to identify the key areas for this analysis and relevant administrative policy documents, I first conducted an environmental scan of the contents of the Health Canada website. I aggregated information from this scan into an overview document that described the key regulatory steps and processes undertaken by Health Canada to manage prescription drugs and that could apply directly or indirectly to off-label prescribing. This overview document included the mandates of different regulatory branches, key definitions, the role and content of the Product Monograph, drug surveillance strategies, information on the Summary Basis of Decision, post authorization activities and detailed information about the Canada Vigilance Program. The Canada Vigilance Program collects and assesses suspected adverse reaction reports that are submitted voluntarily by consumers and healthcare professionals in Canada and by drug manufacturers and distributors (see Section 5.5.2)

The third source of information used for the policy analysis involved three sets of contacts with officials from Health Canada's Marketed Health Products Directorate. One of these contacts involved a lengthy telephone interview with a Scientific Advisor from MHPD which centred around questions I submitted in advance. Two additional contacts were undertaken with staff from MHPD that involved my submitting a set of questions in advance which were responded to in writing by MHPD. The focus of these discussions was to clarify the meaning, intent and scope of particular policies and their real or potential relationship to off-label prescribing and specifically to the off-label prescribing of domperidone to treat LMS.

Three Canadian drug safety/legal experts were also contacted by email to determine whether there were key Health Canada policy areas that they felt warranted consideration (another expert was contacted but did not respond). Two experts provided more detailed advice on policy identification and interpretation. One of these experts, a lawyer specializing in Canadian health policy, provided information on the implementation and interpretation *Bill C-17* as it might relate to off-label prescribing.

Information from these sources as well as from the overview document helped determine the key policy areas to be considered in the policy analysis. These key areas included: aspects of the drug approval process; post -market surveillance; risk communication and new Ministerial powers related to drug safety included in *Bill C-17*. These policy areas are described in Table 34. Any explicit or implicit references to off-label use in these policy areas are identified and discussed. If references to OLU are missing in the policy area, these gaps are noted.

Canada's *Food and Drugs Act*, an act of Parliament and its related regulations, provides the legal context, mandate and standards for the testing, approval and safety of drugs in Canada, as well as a regulatory mandate for food and cosmetics (35). The *Food and Drugs Act* also mandates Health Canada to approve drugs (Therapeutic Products Directorate or TPD and Biologics and Genetic Therapies Directorate or BGTD) and the Marketed Health Products Directorate (MHPD) to undertake post-market surveillance.

In most cases, this section does not discuss or analyze the specific regulations under the *Food and Drugs Act* that relate to the policy areas I selected for inclusion in this analysis (see Table 34). Instead, my analysis focused primarily on guidance and other policy-related documents that describe and interpret policies, government statues and regulations that promote a consistent interpretation and compliance with the Act.

I chose this focus because I was most interested in how policies were being described and interpreted by Health Canada and transmitted to professionals and industry to promote compliance under the Act with regard to drug safety and efficacy. Guidance documents are considered by Health Canada to be administrative instruments rather than legal documents. As such, they allow for some flexibility in interpretation, if this is supported by 'adequate scientific justification'.

There was one exception to this reliance on policy documents. I discussed new regulations related to *Bill C-17* (*Vanessa's Law*), an Act that amended the *Food and Drugs Act* that was proclaimed in 2014. The amendments included dramatic changes to the powers of the Minister of Health to withdraw a drug or take other measures in response to a drug that is considered to present risks to the health of Canadians. This Act has been one of the most substantial amendments to the *Food and Drugs Act* in relation to drug safety.

Table 34: Policy Areas and Documents Reviewed in the Policy Analysis

Policy Area	Documents Reviewed	Description
Drug Approval	• Product Monograph: Guidelines for content • Sample Monograph: Domperidone Product Monograph	• A Product Monograph (PM) is prepared by MAH or Market Authorization Holder with guidelines set by Health Canada. It must be approved by Health Canada prior to a drug being sold. • The PM includes clinical trial data, drug characteristics, uses, potential ADRs and contraindications. • The policy analysis examined whether PMs reference off-label uses.
Post-Market Surveillance	• ADR reports from industry, voluntary reports • Canada Vigilance Database • Identification and response to safety signals • Domperidone Safety Reviews	• Health Canada continues to track drug safety issues after market approval using a variety of methods (post-market surveillance). Four post-market surveillance activities are discussed in this section.
Risk Communication	• Health Canada advisories on domperidone	• This section describes the characteristics of risk communication messages mandated by Health Canada and whether they reference off-label prescribing or the OLU of domperidone.
Ministerial Authority as Defined in *Bill C-17* (*Vanessa's Law*)	• The F&DA (broad overview) • *Bill C-17*	• This section provides background on *Bill C-17* and the new legal and regulatory environment within which drug safety issues are addressed. The focus is on new and pending Ministerial powers to order new tests and assessments from the MAH if a drug safety issue is identified and the ability to order label changes or withdraw the drug, if required.

I included an assessment of policy-related documents such as the Health Canada minutes from a key meeting of Health Canada officials. I also integrated comments from MHPD officials and Canadian legal/policy experts in the analysis in order to clarify the meaning and application of some of the policies.

5.4 Approach Used to Analyze Policy Documents

A systematic method of content analysis was developed and used to analyze and report the data arising from the policy analysis (208-209). I developed a hard copy and Excel data entry format to use as a content guide for reviewing the policy documents and to ensure the entering of comparable data.

Each policy or related document was reviewed two to four times. General notes were taken on major themes, conclusions and additional questions before summary data was entered onto the template. I also incorporated relevant comments about Health Canada policies that were made by key experts and Health Canada officials onto these records.

There were four factors that affected the policy analysis. The most significant was the almost total lack of explicit reference to off-label prescribing in the administrative, legal/regulatory and related documents that I reviewed. In some cases, approved uses are specified in the policy or regulatory document, in other cases, the approval status of a drug product was not specified. In other cases, the ambiguity of language made it difficult to ascertain if a policy or regulation did apply to OLU. This ambiguity was also reflected in my interviews with Health Canada officials.

Secondly, the Health Canada website was not easy to search in a consistent and efficient way. Documents can be removed and updated and it is sometimes difficult to trace their trajectories. One key policy document, for example, was removed several months after I had incorporated it into my research but when I tried to retrieve it, was not available, even in an archived form.

When there was a lack of clarity about a policy, I contacted Health Canada officials for assistance. This communication was frequently delayed by weeks or months and in many cases, the answers provided simply led me back to existing documents on the Health Canada website, with no further clarity on the interpretation of the policy.

Finally, there was a lack of transparency related to the two Safety Reviews (Signal Assessment Addenda) conducted by Health Canada on the assessment of domperidone's association with serious ventricular arrhythmias and sudden cardiac death (210, 211). Safety Reviews are triggered when signals from ADRs or other information indicate that there are potential safety issues with a drug or drug class. Although Safety Reviews are publicly accessible, it took four to six months before Health Canada made them available to me. Both of the reviews were heavily redacted, for example, over 70% of the content in one of the reports was blacked out. Health Canada informed me that the extensive redactions were needed in order to protect the 'commercial business interests' (CBI) of the MAH. The legal right of Health Canada to block access to the public and researchers to information about the safety of drug products for reasons of CBI has been raised as a concern by a health policy legal expert in Canada (212).

5.5 Findings from the Policy Analysis

This section presents findings from the analysis of Health Canada policy documents in the areas of drug approval (Product Monograph), post-market surveillance (collection of ADRs, signal analysis, Canada Vigilance database, Safety Reviews), risk communication and the Minister of Health's new authority under *Bill C-17* (*Vanessa's Law*). In this chapter, each document is described separately or clustered with other similar documents using the following content headings: content and target group of each document, its applicability (if any) to off-label prescribing, and concluding comments about its use and relevance. The goal of this chapter is to determine whether and how each policy document references or is applicable to off-label prescribing.

5.5.1 Drug Approval Policies (Drug Monograph)

The drug approval process involves many steps including the decision of a pharmaceutical company to apply to the Health Products and Food Branch (HPFB) for authorization to conduct clinical trials to establish a drug's dose, quality and effectiveness. If a drug is seen to have therapeutic value, the manufacturer can file a new drug submission to the HPFB which then evaluates the safety and efficacy of the drug product as well as the quality of the manufacturing process. If this review concludes that the benefits of the drug outweigh the risks and that the risks can be mitigated, the drug can be issued a Notice of Compliance (NOC) (compliance with the marketing conditions in the F&DA) as well as a Drug Identification Number (DIN) which allows it to be sold in Canada.

Although drugs can be tested by drug manufacturers for some off-label indications, there is no assurance that they have gone through the complete clinical trial process unless the company applies for approval and the drug is rejected for that indication. Up until March 2019, Health Canada did not release information about indications that were not approved.

I focused on one component of the drug approval process - the development and contents of the Product Monograph (PM). The PM is one of the key elements of the drug approval process. The PM provides information for the public and healthcare professionals on the drug's indications, safety and efficacy. Product Monograph content is regulated by Health Canada and many PMs are accessible on Health Canada's website. The PM is based primarily on data submitted by the drug company sponsor and is evaluated by Health Canada as part of the regulatory drug review and authorization process. It becomes part of the Notice of Compliance (NOC) for a new drug submission. A drug manufacturer receives a NOC for a specific drug when it has met Health Canada's requirements for drug efficacy, safety and manufacturing quality.

I reviewed five policy and policy-related documents related to Product Monographs. These focused the general content of PMs or PMs specifically related to domperidone. The documents were:

- Health Canada. Guidance Document on Product Monographs. This document provides guidance to drug sponsors on how to develop the content and format for Drug Monographs (213);
- Health Canada. Frequently Asked Questions: Product Monograph. This document provides an interpretation of the Guidance Document (214);
- Health Canada. Health Products and Food Branch Bilateral Meeting Program: Agenda Item Summary– Disclaimers in Product Monographs. April 5, 2012. This document discusses how Health Canada has some flexibility in determining the language in Product Monographs (215);
- The Product Monograph for Apo-Domperidone prepared by Apotex Inc. (116). Apotex Inc. is one of the main manufacturers and sellers of the generic form of domperidone. I included the Apotex PM as an example of the content that is mandated by Health Canada. I also reviewed a second PM for another drug to see if cautions about off-label prescribing were included (216);
- Health Canada's Guidance Document for Product Monograph Content: Release of Revised Version of Health Canada's QT/ QT_c Interval Prolongation. This document was withdrawn by Health Canada but raises relevant points about QT-prolonging drugs like domperidone (217).

Guidance Document on Product Monographs, FAQ Document and Meeting Minutes

Description of the policy document, objectives and target group

Health Canada's Product Monograph Guidance and a related FAQ document (213, 214) provide information to the MAH on the content of the PM required by Health Canada. The PM must include specific information about the drug's name and therapeutic classification, its actions, approved indications, contraindications, dose, administration, warnings, precautions, adverse reactions, drug interactions, handling instructions, information on clinical trials, overdosage symptoms, responses and toxicology.

The PM also provides information on the drug's characteristics and potential ADRs in sections addressed to patients/consumers and health providers. Product Monographs provide the most accessible and comprehensive information about an approved drug product that is available. Product Monographs provide most of the information included in the Compendium of Pharmaceutical Specialties (CPS), a prescription drug reference resource commonly used by Canadian healthcare professionals. However, Health Canada notes that the Product Monograph does not include all information or evidence about a drug:

> ‘The Product Monograph is not intended to serve as a repository of all information currently available on a drug. The Product Monograph is based primarily on data submitted by a sponsor and evaluated by Health Canada as part of the regulatory drug review and authorization process. As a result, it may not reflect the entire existing body of evidence’ (213: Sec.:1.3).

Product Monographs for generic drugs are duplicates of the PM for the original brand name product because the generic form is bioequivalent to the brand name drug. As part of the new regulatory powers under *Bill C-17*, the Minister of Health may request that the drug sponsor revise the PM for a specific drug if new information indicates that changes to safety information is required or whenever substantial information is available that would suggest new indications.

Does the Product Monograph Address Off-label Prescribing?

The Health Canada guidelines on the required content of Product Monographs specifies that these documents reference only the approved uses of a drug, described as,

> ‘ . . . only those indications and clinical uses that are based on substantial evidence of efficacy and safety and that are subject of a New Drug Submission, or an Abbreviated New Drug Submission, or a Supplement to either submission that has received a Notice of Compliance pursuant to Section C.08.004 of the Food and Drug Regulations, should be included in the product monograph’ (214: p.1).

In cases where a drug has been marketed and then is prescribed off-label these uses could be identified if this data were collected in the post-market surveillance period. Where safety risks are identified in this data, the language in the PM could be modified. Health Canada’s most recent safety report on domperidone (211) recommended strengthening the language on safety in the PM although these recommendations were made for approved indications. Discussions with MHPD were unable to clarify whether these recommendations were followed. Officials from Health Canada confirmed that the indications addressed in a PM are ‘the medical conditions for which the drug has been authorized for sale in Canada’ and ‘that the use of domperidone as a galactogogue is not part of the indications for domperidone use’ (Personal communication, MHPD, January 7, 2019).

Although Health Canada guidance on the content of PMs only considers approved indications, the following guidance seems highly relevant to the off-label use of domperidone to treat LMS by breastfeeding mothers. This guidance document specifies that:

> ‘Unless studies have shown that the product is not excreted in human breast milk the following or similar statement should be included: Where an assessment of the risk to benefit ratio suggests the use of this product in nursing mothers, formula feeding should be substituted for breastfeeding’ (213: p. C6).

Despite statements from Health Canada that the PM is focused on approved indications, there is some ambiguity in guidelines about this policy. The minutes of a bilateral meeting between the HPFB and the Pharmaceutical Advertising Advisory Board that took place on April 5, 2012 (215) was included in this analysis to explore whether all drugs approved on the basis of surrogate markers

include disclaimers about morbidity and mortality. The content of this meeting also addressed the inclusion of disclaimer statements in Product Monographs in general.

At this meeting, Health Canada stated that disclaimers are 'still occasionally used in product monographs as they may provide a better understanding in certain circumstances' (215: p.1). It also stated that statements of non-indication should be avoided in a PM (e.g., Product A does not treat condition B) unless there is a very good rationale to do so. According to Health Canada, the reason for not routinely including non-indications in the PM is because, 'Lists of non-indications clutter the text, contribute to confusion, and may be incorrectly recalled later by a prescriber as an actual indication' (p.2).

Health Canada officials attending this meeting acknowledged that 'non-indications are still found in many Product Monographs and will continue to be added to the PM, based on an individual assessment of each product and negotiation between the sponsor and the regulator, where some benefit is expected from the text' (p.2).

Key Summary Comments

The completion of the PM by the MAH, as mandated by Health Canada, is a necessary step in the drug approval process. The PM provides the most comprehensive information on a drug that is available to healthcare providers and the public but does not include all information. The contents of a PM are prepared by the MAH. The content in the PM is based on the Health Canada approved indications of the drug. However, the PM could be modified post-approval to include guidance about using the drug for off-label uses.

Product Monograph: Apo-Domperidone (domperidone maleate)

Description of the Policy Document, Objectives and Target Group

Health Canada has authorized multiple pharmaceutical companies to sell the generic version of domperidone. Each manufacturer is required to submit a PM following the content guidelines specified by Health Canada described above. I reviewed one current PM for a generic version of domperidone-Apotex Inc. (116) in order to determine whether there was any reference to the drug's off-label use as a galactogogue. The Apotex Drug Monograph provides information to health professionals and patients about domperidone's uses, safety and efficacy as required by Health Canada. The indications for apo-domperidone that have been approved by Health Canada and that are listed in the Apotex PM are for the 'systematic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis' and 'to prevent gastrointestinal symptoms associated with the use of domperidone agonist antiparkinsonian agents' (116: p.4). No off-label indications for domperidone, including for the treatment of LMS, were referenced in this PM.

I was unable to ascertain if generic companies have to modify the PM if the brand name product is no longer being sold. The evidence suggests that if Safety Reviews (211) recommend changes to the language in the PM about the safety of a product that is in generic form only, those changes will be likely be made in the PMs for the companies selling the product in generic form but I was unable to confirm whether this occurred in all cases.

Does this Policy Document Address Off-label Prescribing?

The Apotex PM included discussions on the potential of domperidone to increase the risk of serious ventricular arrhythmias or sudden cardiac death that could apply to domperidone; however, no off-label uses were specified. It also described an increase in risk when doses of domperidone of more than 30 mg/day are used, when the drug is used concomitantly with other drugs that prolong the QT-interval, or used in patients with significant electrolyte disturbances or underlying cardiac disease. The PM also recommended that domperidone be used at the lowest possible dose for the shortest period of time. These warnings were not specified as applying to domperidone when it is used to treat LMS.

Key Summary Comments

The Apotex Inc PM for Apo-Domperidone referred only to the approved indications for the drug. Off-label uses such as the use of domperidone as a galactogogue were not included.

To determine whether Heath Canada has ever exercised this flexibility, I reviewed another Product Monograph where a literature search suggested an off-label use of a drug where its risks had been described in conjunction with that off-label use. This PM was for Paxil CR which was submitted to Health Canada by GlaxoSmithKline and revised in March 2018 (216). Paxil is a Selective Serotonin Reuptake Inhibitor (SSRI) which is prescribed for depression, anxiety and other mental health problems.

The PM for Paxil CR focused primary on approved indications but also included a statement saying that the drug is not indicated for use in patients below the age of 18 – an off-label use. I did not examine the historical triggers to this reference to off-label prescribing in the Paxil PM or the relationship between warnings issued by Health Canada on the off-label use of the drug and how this might affect the language in the PM. Therefore, the caution against using Paxil CR in those under 18 may have been present in the original PM.

Policies about including references to off-label prescribing in PMs are difficult to establish. The most recent safety advisory on domperidone suggests that Health Canada can broaden the language in warnings to include unspecified off-label uses. There is a lack of clarity on when and why this occurs and I was unable to clarify this in my communication with Health Canada officials.

Revised Version of Health Canada's QT/ QT_c Interval Prolongation: Guidance for Product Monograph Content (Withdrawn)

Description of the Policy Document, Objectives and Target Group

This guidance document, now withdrawn, provided instructions to MAHs on the content of Product Monographs if the drug affected the QT/ QT_c interval (217). I reviewed this document prior to it being withdrawn from Health Canada's website. This document was effective 2010/03/31 but I was unable to determine the date of withdrawal or find it in the archives section. According to Health Canada, the reason for withdrawing this guidance document was because it is 'no longer reflective of current practices, science and/or policies.' Health Canada officials told me that the risks associated with QT-prolonging drugs are now included in individual PMs rather than in a broad guidance document.

This (withdrawn) Guidance Document provided information on Program Monograph content on topics such as the characteristics and outcomes of QT-prolonging drugs, the range of drugs to which the guidelines applied, indications and contraindications of use (with particular importance to cardiovascular effects), drug-drug interactions that could result in an exaggerated prolongation of the QT interval, including the risks of using concomitant QT/ QT_c -prolonging drugs, dose and pharmacology information and independent risk factors that could make an individual more susceptible to the harms associated with a QT-prolonging drug.

Does this Policy Document Address Off-label Prescribing?

This withdrawn policy document describing required PM content when a QT-prolonging drug is involved did not specifically require any reference to the off-label uses of QT-prolonging drugs. However, this document did explicitly identify female gender as an independent risk factor when a QT-prolonging drug is used. Female gender is not included as an independent risk factor in the Apotex Product Monograph for domperidone although the Apotex Monograph was issued after this guidance document was developed. (I was not able to clarify whether generic companies are required to modify PMs if the brand name drug has been withdrawn from the market.) This may indicate a gap in the identification of potential safety information related to QT-prolonging drugs. However, a review of multiple PMs was not conducted to verify whether gender has been included as an independent risk factor in PMs for QT-prolonging drugs.

Key Summary Comments

All QT-prolonging drugs pose heightened cardiac risks and specific independent risk factors have been well defined. This Guidance Document, now withdrawn, offered specific direction to MAHs on the content of PMs when a QT-prolonging drug is approved. This withdrawn document included female gender as an independent risk factor and stressed the inclusion of concerns that could be

relevant to women in the reproductive age group as well as the risks of taking more than one QT-prolonging drug concurrently.

When asked about withdrawing this guidance document on the risks of QT-prolonging drugs, Health Canada officials suggested that product-specific risks are normally addressed through Health Canada's risk management plans (RMPs) rather than through PMs. (Personal communication, MHPD, March 7, 2019). RMPs are not publicly available. In relation specifically to the cardiac risks of domperidone as a QT-prolonging drug, officials noted that they had reviewed domperidone's safety issues within two safety reviews and, in response to their conclusions, had strengthened the language in the domperidone PMs to 'better inform Canadians on the risk of serious ventricular arrhythmias and sudden cardiac death' (Personal communication, MHPD, July 19, 2019). The officials provided a list of common risk factors and conditions that applied to domperidone use and were included in the PMs. Female gender was not included as a risk factor in these lists although age (over 60) was.

A focus on identifying risks through risk management plans rather than within a PM may be one of the reasons why Health Canada no longer appears to offer standardized guidance to MAHs on addressing the risks of all QT-prolonging drugs. The exclusion of gender as an independent risk factor in relation to domperidone is a concern and has important implications for women in the reproductive age group who are taking a QT-prolonging drug.

5.5.2 Post-Market Surveillance

After a drug has been approved, Health Canada continues to monitor its safety through a range of post-market surveillance activities. The post-market surveillance of prescription drugs is critical to ensure drug safety because the testing of drugs during the pre-approval clinical trials phase involves only a relatively small number of subjects who usually take the drug for a short period of time. Post-market surveillance enables the monitoring of drug safety among the wider population which is larger, more diverse and where patients are using the drug under different conditions. Post-market surveillance is a long-term endeavor because many drug safety issues may not emerge for many years (218-220).

This section examines policy documents related to four post-market surveillance activities: the collection of ADRs from industry and voluntary sources, the reporting of ADRs on Health Canada's Vigilance Database, safety signal detection and the interpretation and responses to safety signals. I describe one type of response used by Heath Canada to respond to a safety concern resulting from signal detection. Drug Safety Reviews are undertaken by Health Canada when data from ADRs, the scientific literature or information from other jurisdictions identify a safety problem with a drug. These reviews include a description of the safety issue and the data on which safety concerns are based as well as options and recommendations for a response by Health Canada. Health Canada has completed two Safety Reviews of Domperidone (210,211) focused on the drug's potential risk for

ventricular arrhythmias and sudden cardiac death. Policy and policy-related documents related to these four post-market surveillance activities are reviewed in this section with a focus on the degree to which off-label uses or the off-label use of domperidone to treat LMS are addressed.

Two major problems were encountered when analyzing policy documents related to these post-market surveillance activities. There was a lack of transparency in terms of how drug safety signals are interpreted and a lack of access to the full content of the Domperidone Safety Reviews. Although Safety Reviews are publicly available, the domperidone reports were sent four months after my request and were heavily redacted so that it was impossible to ascertain the full extent of domperidone's safety problems or how Health Canada proposed to address them.

i. Reporting of ADRs

Post-market surveillance is heavily dependent on the submission and analysis of ADR reports which are collected by both MAHs and submitted to Heath Canada and by Health Canada through voluntary reports made by the public and healthcare providers. The collection and interpretation of ADRs is regulated under the F&DA and coordinated by the MHPD. After ADR reports are collected, they are analyzed by Health Cto identify safety signals that may trigger a further need for analysis which can lead to additional responses. Responses can include Health Canada conducting more detailed Safety Reviews or undertaking other regulatory responses such as making changes to the product's label, issuing a risk communication to the public or healthcare providers or withdrawing the drug (221).

Canada's Food and Drug Regulations define an adverse drug reaction as 'a noxious and unintended response to a drug which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function' (221). Adverse drug reactions can occur immediately or be delayed. They can be minor or serious and life-threatening. A serious adverse drug reaction is defined as a reaction that 'requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life threatening or that results in death' (221). ADR reports are not intended to define a causal relationship between a drug and an adverse reaction but to identify suspected relationships.

Historically, the highest proportion of ADR reports submitted to Health Canada have been made by MAHs which are mandated to do so. Health Canada also collects voluntary reports. Reports from industry and voluntary reports can be from healthcare providers and consumers. Voluntary reports can be submitted by mail, online and through telephone submissions to Health Canada's regional Canada Vigilance offices.

A recent analysis (April 2020) of ADR reporting in Canada indicates that the source of reporting has recently shifted to include a higher proportion of reports from clinical studies. Reports

from clinical trials differ from the 'real-world' conditions under which voluntary reports and reports from MAHs are made. However, in an analysis of these different reporting sources, the authors found that, 'A 10-year average of most ADR indicators, such as the rate of serious outcomes, top ADR drugs and disease indications, did not exhibit any substantial difference between the two groups' (222: p.41), suggesting that the results from spontaneous ADR reporting are the same as those from clinical trials.

This chapter focuses primarily on systems for collecting data through voluntary reporting and through MAHs which was the original focus of my research and which is based on a set of policy documents and guidelines used by Health Canada. Canadian hospitals have also recently been mandated to submit ADR reports. Because this program has only recently been implemented (December 2019), the ADR results from hospitals are not included in my analysis.

ii. Mandatory ADR Reports Submitted by Industry

Description of the Policy Document, Objectives and Target Group

Regulations under Canada's *Food and Drug Act* (FDA) specify that MAHs (Market Authorization Holders) are required to report serious domestic and foreign ARs to the MHPD. A Health Canada Guidance Document and related information (223, 224) provides MAHs with assistance on how to comply with these requirements.

ADR reports submitted by MAHs to Health Canada are completed on forms with pre-defined categories. These forms collect information on patient characteristics, including age, gender and existing medical conditions, the report source, the name of the drug product, DIN (Drug Information Number), dose taken and information about the ADR, its duration, seriousness and outcomes, including whether the patient recovered, died or recovered with sequelae (224). Information about the identity of the patient and the health care provider are kept confidential. MAHs are required to submit ADR reports on serious adverse reactions to Health Canada within fifteen days.

Does this policy address off-label prescribing?

Information on whether an ADR is associated with a drug being prescribed off-label is not collected on the ADR reporting form submitted by MAHs. A question on the mandatory reporting form asks reporters to provide the reason why the drug was prescribed to the patient (223, 224) and the drug suspected of causing the ADR. However, there is no question that identifies whether the drug being prescribed was for an indication for which it has not been approved. This could be ascertained by Health Canada linking the indication entered on the form with the DIN number for the drug to determine if this is an approved use, however, there is no expectation that this information be collected.

The lack of clarity on the indication of the drug as reported in industry ADR reports was affirmed in discussions with officials from MHPD. They stated that quality of information collected on

the indication of a drug is dependent on the reporter completing the ADR report. Reporters could be consumers or health professionals. Research suggests that health professionals and the public are not always aware when a drug is being prescribed off-label (22, 48, 49).

Health Canada officials stated that there was currently no plan to systematically collect information on off-label uses in ADR reports in the future because it is not a regulatory requirement. However, information on whether an ADR report resulted from an off-label use can be entered in the Canada Vigilance database if the reporter knows and provides it. They also stated that, for "ad hoc safety issues, if off-label use is a possible factor to consider in the analysis of the safety issue, it will be included in the over-all analysis" (Personal correspondence, MHPD, March 7, 2018). Health Canada also indicated that the MAH may be contacted for follow-up information on reports if off-label use is considered to be a factor and there is a safety concern. The degree to which this takes place is unknown.

Summary Comments (Industry Reports)

Historically, MAHs have submitted the majority of ADR reports to the MHPD. These reports are derived from health professionals and consumers. The reporting form submitted by industry to Health Canada contains information about the drug product associated with the ADR, the DIN, and the general reason why the drug was prescribed. However, there is no data clearly establishing whether the ADR is associated with an approved or unapproved use of the drug.

Although Health Canada has acknowledged that the quality of the reports depends on the quality of the reporter, reporters, (primarily healthcare providers and the public), may not know whether the drug has been used for an unapproved or approved use. Despite there being some willingness to consider whether ADRs are linked to off-label uses, there appears to be no clear Health Canada policy which would instruct industry to systematically collect this information.

iii. Voluntary Reports Submitted by Healthcare Providers and the Public

Description of the Policy Document, Objectives and Target Group

Health Canada enables Canadian healthcare providers and members of the public to submit voluntary ADR reports to MHPD online or through their national and regional Canada Vigilance offices. Health Canada provides policy direction on the content and submission of these voluntary reports (225, 226).

The forms for the voluntary reporting of ADRs by the public and health professionals are comparable to those completed by MAHs. These reports collect information about the reporter, the medical history of the person experiencing the ADR, the characteristics, timing and duration of the effect, information about the product and the likelihood of the product causing the ADR. Information is also collected on the medical history of the person with the reaction, its seriousness, outcome, dose and origin of the product, including online access.

Does this policy address off-label prescribing?

The voluntary reporting form available from Health Canada has one question which asks for the reason why the drug was prescribed. While this provides information about the indication, there is nothing on the form that would verify whether the indication is associated with an approved or unapproved use of the drug. However, if information about the indication for which the drug was used was matched with the drug product information, which describes the drug's approved indications, this could be determined by Health Canada.

Summary Comments

In 2017, there were 56,983 mandated Canadian ADR reports but only 8600 voluntary reports (227). Hohl et al. (228) have raised concerns that if *Vanessa's Law* is to successfully address drug safety problems simpler, faster and more user-friendly ADR reporting forms need to be developed and used by Health Canada.

Although voluntary ADR reports from Canadian consumers and healthcare providers collect information on the health problem for which the drug was prescribed, reports do not include whether the drug being used to address the condition and which is associated with the ADR is being used for an unapproved indication. It is probably not realistic to assume that the public would know whether a drug is being used for an off-label indication. Health Canada officials have indicated that they have no plans to systematically collect information that would determine whether a drug associated with an ADR was associated with an unapproved indication. in either mandated or voluntary reports in the future even though they might analyze whatever data is available in an ad hoc way. The circumstances when this occurs or the frequency of this follow-up is unknown.

iv. Policies Related to the Canada Vigilance Database

Description, Objectives and Target Group of the Policy

Another key component of Health Canada's post-market surveillance is the collection and reporting of ADRs in the Canada Vigilance Adverse Reaction Online Database. This database is a repository for information from post-market ADR reports from a variety of sources including mandatory reports submitted by industry and voluntary reports submitted by the Canadian public and healthcare providers described in Sections ii and iii above. A recent analysis of records in the database indicates that there is a growing proportion of ADR reports submitted to the database from clinical studies (222). Two-thirds of the reports submitted to the database have been made in the last decade and between 2009 and 2018 there was a fourfold increase in the reporting rate.

Reports on the database contain relevant information about the patient characteristics and details about the reaction(s) suspected to be associated with the health product(s), the general finding(s), the treatment and final outcome(s). Information about the identity of the patient and the

health care provider is not provided. Reports can be extracted and clustered by filters that include the date of the report, gender and age of the reporter, and type of adverse reaction by specified product. (229, 230). Records from 1965 to 2019-07-31 were included in the database when it was reviewed on September 25, 2019, although it is updated periodically. The database can be searched by the public.

The target group for the database includes the Canadian public, healthcare providers and researchers. However, Health Canada advises caution in interpreting suspected ADR report data due to factors such as the overall underreporting of ADRs, the fact that reports are comprised of suspected associations which reflect the opinions of reporters, the potential inclusion of duplicates and the inability of reports to establish causal relationships. Until May 2019 duplicate reports (the same reports submitted by different reporters) were not identified in the database.

Does this policy address off-label prescribing?

ADR reports entered on the Canada Vigilance Adverse Drug Reaction Database do not systematically include information on whether an ADR being reported relates to an approved or unapproved drug use. My review of a small sample of ADR reports on domperidone in the database found that some reports included information that specified the drug with the associated ADR was being used off-label. By applying a filter to designate women in the reproductive age group, a further analysis of the database might be able to identify reports involving the use of domperidone when it is being used to treat LMS.

However, without a more extensive survey of the database, there was no way of determining how frequently this information is included in the reports. Health Canada has stated that this information is included in the database when it is provided by the reporter but inclusion of this information in reports appears to be sporadic.

Summary Comments

According to Health Canada, when a reporter of an ADR specifies that drug associated with the ADR involves an off-label use, it may be entered in the Canada Vigilance online database but there is no requirement to provide it. There is no specific question on the reporting form that requires the reporter to make a link (if they could) between the drug and whether it was prescribed for an approved or unapproved indication Although some ADR reports of domperidone on the database indicate that the ADR was associated with an off-label use of the drug, Health Canada officials were unable to tell me why or under what circumstances this information was provided, except to say that the information in the report depends on the reporter. However, putting the responsibility for clearly identifying off-label use on the reporting forms on reporters like healthcare providers and the public so that the data can be entered into the Canada Vigilance Adverse Drug Reaction database suggests that Health Canada does not view the collection of this data in a more rigorous way as a priority. The

limitations of the database raise concerns about its capacity to identify important safety issues related to the off-label uses of any drug, including domperidone.

v. ADR Signal Detection

Description, Objectives and Target Group of the Policy

ADR reports are analyzed by Health Canada to identify signals that may indicate potential drug safety problems. A signal is considered to be the preliminary indication of a drug-related issue which triggers a need for further investigation of the drug. The evaluation of signals is required before any pharmacovigilance actions are undertaken.

According to Health Canada, signals are detected through the periodic analysis of the information contained in the Canada Vigilance Database. Statistical monitoring strategies and tools are used to identify signals. These include tools developed by other agencies such as the WHO. Additional investigative studies and data from other regulatory agencies are often used to confirm the association between the drug and the ADRs. However, there is a lack of clarity on how these tools are applied by Health Canada to determine signals that reflect safety concerns.

Statistical tools such as Standardized Medical Queries (SMQs), using terms such as Torsades de Pointes and ventricular tachyarrhythmias, were used to identify safety signals in relation to domperidone as reported in one of the Health Canada's Safety Reports on the drug; however, I was unable to establish who conducted these analyses (211).

The determination of a signal indicating a drug safety problem also involves assessing the quality of information included in ADR reports. This includes when the ADR occurred and its appearance or reappearance if the product is discontinued and then reintroduced. Other information includes patient characteristics such as their underlying illnesses and their use of other medications. According to Health Canada there is no required number of ADR reports that are necessary to determine a safety signal.

Does This Policy Address Off-label Prescribing?

A signal indicating a safety problem is determined through an analysis of ADR reports and supplementary information. Because information on off-label uses of drugs is not routinely collected by Health Canada in ADR reports, it is not clear how or to what degree off-label uses are considered in signal assessment processes.

Summary Comments

The analysis of ADR reports submitted to Health Canada is used to detect signals that may indicate a drug safety problem and trigger a need for further analysis or a pharmacovigilance response. Regulatory responses can include the implementation of a Health Canada Safety Review of

the drug, the issuance of a risk communication message to healthcare professionals and/or the public, the Minister of Health ordering drug label changes or removing the drug from the market.

Health Canada's process for identifying and interpreting signals in order to determine a drug safety issue is not transparent. Health Canada provides no information on the scope and content of information that contributes to a signal detection. Hohl et al. (228) also note that specific ADRs may not be identifiable in large datasets unless broad algorithms are used which may have low specificity.

vi. Drug Safety Reviews

Description of the Policy, Objectives and Target Group

MHPD can conduct a Safety Review of a drug or drug class as part of post-market surveillance when the analysis of signals or other data indicates there is a safety problem. Safety reviews can be triggered when the serious side effects associated with a drug occur more frequently than expected, unexpected side effects arise or they are occurring in vulnerable populations such as in children or pregnant women.

Safety Reviews involve compiling and assessing all the available information on the safety of a specific drug or drug class. This includes updated clinical and non-clinical information on the safety issue being examined (often including new signal assessments arising from ADR reports), specific investigations or responses to the safety issue by other regulators, causality assessments that attempt to link factors such as dose and age with the safety concern and updated reviews of the drug in the scientific literature. I could not find information from Health Canada on how these sources of information were weighted in a Safety Review.

Safety Reviews also include options for responding to the safety issue, a discussion of the pros and cons of these options and recommendations drawn from these options which are put forward by the MHPD to the Therapeutic Products Directorate (TPD) or Biologics and Genetic Therapies Directorate (BGTD) (hereafter collectively referred to as the TPD) for consideration and action. Recommendations can include changes to the Product Monograph, the issuance of risk communications, plans to carry out further studies on the drug and the drug's withdrawal from the market.

Although MHPD drafts the policy recommendations for the Safety Review, it is the responsibility of the TPD to see that they are implemented. Many of the policy recommendations are within the mandate and responsibility of the MAHs to implement. The TPD works collaboratively with the MAHs to implement the recommendations although the exact nature of this collaboration is unclear. According to Health Canada, there is follow-up by MHPD to determine whether the recommended changes have been made, however, I was not able to determine to what degree any of the recommendations made in the two Safety Reports on domperidone's cardiac risks were implemented.

MHPD conducted Safety Reviews of domperidone both dated in 2014 (210, 211). Both reviews were focused on the safety of domperidone in relation to serious ventricular arrythmias and sudden cardiac death. The purpose of the first review was to summarize new data related to this issue, determine whether this new information warranted a regulatory response and to make recommendations to Health Canada management on what this would include.

It was difficult to analyze the content of the first Safety Review (210) because approximately 70% of the report was redacted. The content that was readable described comparisons between the content of the current Canadian PM for domperidone with reports of cardiac events related to the drug reported by other jurisdictions. This review concluded that current data supports the association between the use of domperidone and serious VA and SCD and that there is the potential of domperidone to induce QT-prolongation. The report included five options to improve the safety of domperidone use for approved indications, two of which were redacted.

The second and most recent Safety Review (211) was completed following the publication of a benefit-risk assessment of the cardiac safety of domperidone-containing products in the European Union. This assessment led to changes in the EU's domperidone prescribing information as well as recommendations for a more restricted use of the drug (124). The restrictions on domperidone's use described in this report included authorizing its use only for relieving the symptoms of nausea and vomiting, restricting dose levels to 10 mg three times a day and the duration of use for one week. Restrictions also included not prescribing the drug to patients with moderate or severe impairment of liver function or with abnormalities in the electrical activity in the heart or heart rhythm and not using it in conjunction with other drugs that affect the heart or reduce the breakdown of domperidone in the body. Although the guidelines included in the European Medicines Agency report did not specifically identify domperidone's use outside of licensed applications, they were intended to be considered whenever domperidone was used.

Two new CV database searches using SMQs were conducted for the second Safety Review. Organizations representing healthcare providers were also surveyed to solicit their opinions on the use and potential risks/benefits of domperidone. This Safety Review concluded that the cardiac risks of domperidone were well established, that dose levels for domperidone for all uses were generally high and appeared to be related to cardiac risks, that the OLU of domperidone for lactation is likely to continue and that Canadian safety advisories were not currently in line with some other drug regulators, particularly the EU. As noted in the review:

> 'While full alignment with the EU prescribing information [restriction of dose, indication and duration of treatment] is not feasible as the Canadian indications are for chronic conditions, it would be possible to lower the recommended daily dose, add contraindications to use in patients at high risk of QT_c prolongation, and encourage limited duration of use. Thus, the status quo is not considered an optimal approach to mitigate cardiac risks associated with domperidone' (211: p.53).

Does This Policy Address Off-label Prescribing?

Although heavily redacted, the first Safety Review (210) noted three off-label uses of domperidone, including the stimulation of milk production. The report also referenced information from the French Medicines Agency that posted a warning/information notice on its website that the OLU of domperidone to stimulate milk production must not be used during breastfeeding. It was impossible to determine whether any of the recommendations for action arising from this review involved the OLU of domperidone.

The second Safety Review (211) acknowledged the regular use of domperidone off-label to treat LMS and included a more extensive discussion of domperidone as a galactogogue. Data from the IMS/Brogan database discussed in this report indicated that there were just over two million prescriptions of domperidone in 2013 and that domperidone was 69th out of the 100 top drugs prescribed in Canada. IMS Brogan is a private company that researches and provides information on the healthcare industry and drug utilization to organizations like Health Canada for a fee. Seventy percent (70%) of the prescriptions in this dataset were for females and 10% were for females of childbearing age.

Reviews of several databases including the Canadian Disease and Therapeutic Index and that of IMS Health Canada Inc., found that mentions of domperidone as a galactogogue were limited. The data from these sources led Health Canada to conclude that it was not possible to accurately quantify the degree of OLU of domperidone in Canada. A review of the medical literature conducted for the review also concluded that dose levels for domperidone when used as a galactogogue were generally between 30-60 mg/day but sometimes reached as high as 80 mg/day. A 2011-2013 internal analysis by Health Canada and reported in the Safety Review (211) also found that almost 80% of the prescriptions for the OLU of domperidone were issued by family or general practitioners. The report stated that the College of Family Physicians described the OLU of domperidone by family practitioners as being primarily for lactation enhancement (Sec.3.14.1).

The recommendations arising from this Safety Review focused on strengthening the Product Monograph to better address the cardiac risks of domperidone, clarifying the language related to the maximum safe daily dose (30 mg/day) and recommending a short duration of use. Cardiac screening was recommended for patients with elevated risks of cardiac problems and the importance of reviewing a patient's use of concomitant QT-prolonging drugs was affirmed. Despite the more comprehensive references to the off-label use of domperidone for lactation in this Safety Review, the

recommendations for action made by the MHPD to the TPD were focused only on the approved uses of the drug.

Summary Comments

Health Canada has completed two Safety Reviews looking at domperidone and its risk for ventricular arrhythmias and sudden cardiac death. The OLU of domperidone for lactation was peripherally noted in the first Safety Review (210). The most recent 2014 Safety Review (211) included a more extensive discussion of the off-label use of domperidone as a galactogogue in Canada and suggested that this off-label use was and will continue to be common. This report included the results of current medical research and information from other regulators on the cardiac risks of domperidone for breastfeeding mothers and their babies.

A major problem with both Safety Reviews was the extensive redaction of their contents. In the first report, it was impossible to determine what information had been used to assess safety concerns related to domperidone or to determine if any of the options for addressing safety concerns related to off-label use The second report also had extensive redactions in certain key sections, for example, reports on safety issues, including case reports, related to the drug's off-label use Despite the acknowledgement of OLU in the most recent Safety Report, recommendations for improving the safety of domperidone addressed only the approved uses of the drug.

A major contribution to this lack of transparency in releasing the complete versions of the two Safety Reviews appears to be related to an interpretation by Health Canada that some information found in Safety Reviews is proprietary because it is confidential business information (CBI) which cannot be made publicly available except under certain circumstances. A Health Canada Guidance Document on CBI (231) describes Health Canada's authority to regulate access to CBI in regulatory documents. CBI is defined as information 'that has actual or potential economic value to a person or their competitors because it is not publicly available and its disclosure would result in a material financial loss to the person or a material financial gain to their competitors' (Sect.1.2).

A health policy legal expert has noted that transparency was once a characteristic of the regulation of pharmaceuticals. When the F&DA was passed in 1920 and evidence on drug safety began to be collected, this information began to be treated as company property. This institutionalized practice has sometimes harmed patients as was the case with Vioxx when the drug's risks were not disclosed by the drug manufacturer (212) to Health Canada and other health regulators.

However, under *Vanessa's Law*, the Minister of Health has been given the discretionary authority to 'disclose CBI to a person (individual or organization who carries out functions relating to the protection or promotion of human health or the safety of the public for the purpose of protecting or promoting human health or the safety of the public' (206: p.21.1 (3)(c). Herder (232) suggests that this potential reshaping of CBI was influenced by the narrowing of what constitutes CBI among regulatory

partners such as the European Medicines Agency. Although *Vanessa's Law* has given the Minister of Health the power to disclose CBI if human health and safety is a factor, the author suggests that Health Canada's culture of secrecy may limit the Minister of Health's use of these new authorities.

5.5.3 Risk Management and Communication

Health Canada defines risk management as ' . . . a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, and the assessment of effectiveness of those interventions' (233: p.1). Health Canada engages in a number of risk management activities including the review of ADRs at the clinical trial and post-marketing stages, the review of data submitted by the MAH related to drug approval, the issuance of periodic safety update reports and the management of risk communications to health professionals and the public (234).

Description of the Policy Document, Objectives and Target Group.

The issuance of a risk communication to the public or healthcare providers by Health Canada or by a MAH under the direction of Health Canada is a key part of the post-market surveillance of drug products and of risk management. A risk communication is issued when there is a suspension or recall of a product, when there are important changes to a product's label or monograph (e.g., new warnings or contraindications) or when there are other changes related to the safe and effective use of the drug product. Risk communications are directed towards helping recipients make well informed decisions about the potential risks of a drug.

The scope of risk communication is broad and includes all communication content that addresses risk decisions and behaviour including guidance documents, warnings and publications. This section discusses risk communication warnings and advisories transmitted to the public and healthcare professionals about the potential risks of a drug.

The issuance of risk communication messages involves the identification of type and level of risk, the risk communicator and the urgency of the message. Health Canada and the MAH both have a role in the dissemination of risk communications. Health Canada can issue public advisories, Dear Health Care Professional Letters, Notices to Hospitals, Information updates, foreign product alerts or provide risk information in publications such as the Health Product Infowatch newsletter. MAHs can disseminate industry-issued Dear Health Professional Letters, Notices to Hospitals, Public Communication or recall notices (234).

Health Canada uses a classification system (173) to designate the urgency of risk communication messages as being of high, medium and low urgency depending on the severity of the drug risk being communicated. Two levels of risk are considered. A Type I health hazard refers to a

risk of serious health consequences or death. Type II refers to a risk of temporary adverse health consequences or remote risks of serious adverse effects.

Health Canada defines three levels of urgency in communicating the risks of a drug: high, medium and low. High urgency refers to a Type I health hazard and involves either a recall notice or a Health Canada public advisory. Medium urgency risk communication is the most common type of risk communication. It involves the transmission of safety information requiring rapid communication and where the outcome or potential risk is serious but where the probability of long-term health consequences of an ADR is low (Type II hazard). Medium urgency risk communications include Dear Healthcare professional communications and industry issued public communications. Low risk involves information provided in fact sheets, backgrounders and publications.

Health Canada has issued two sets of medium risk communications on domperidone for health professionals and the public. On March 7, 2012 a risk communication was sent to health professionals via a Dear Health Care Professional Letter (174) and a comparable warning was issued to the public. The 2012 advisories indicated that the risk of abnormal heart rhythms and cardiac arrest may be higher in patients using domperidone at doses greater than 30 mg/day or in patients more than 60 years old. The advisories recommended that domperidone be used with caution if a patient has a heart condition with abnormal electrical activity (QT-prolongation), heart failure or low levels of potassium or magnesium.

The most recent risk communication about domperidone was issued to the general public and to health care providers in January 2015 (127, 170). The 2015 advisory was similar to the 2012 advisories but added moderate or severe liver disease as another contraindicated use and expanded the warning to say that domperidone should not be used if a patient is using other drugs that may change the electrical activity of the heart or increase the amount of domperidone in the blood. This warning stated that if a patient experienced symptoms of an abnormal heart rhythm such as heart palpitations, dizziness, fainting or seizures while taking domperidone, they should stop taking the drug and get immediate medical attention.

Do Risk Communication Messages Address Off-label Prescribing?

The 2012 advisories discussed the indications of domperidone as being for the 'symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis 'and for the prevention of 'gastrointestinal symptoms associated with the use of domperidone agonist antiparkinsonian agents (174: p.1), all approved uses. Off-label uses were not referenced in the advisories.

Although the 2015 warning repeated the information provided in the 2012 warning for approved indications, the wording in the 2015 warning was expanded to say that it applied to, 'patients taking domperidone for any condition' (127: p.1). This change in the wording broadened the warning to

potentially include those taking the drug off-label for any indication, including for the treatment of LMS but these other indications were not specified.

Summary Comments

Health Canada issued two sets of advisories on domperidone to the public and healthcare professionals in 2012 and 2015. While the language of the 2012 advisory focused only on the approved uses of domperidone, the 2015 advisory broadened the scope of the language to refer to the use of the drug by patients for any condition. The 2015 advisory also included additional risk factors and warning signs related to its use. Neither advisory described female gender as an independent risk factor.

Officials from MHPD stated that risk communication generally focuses on the approved indications of a drug. This is because Health Canada describes its role as not overseeing decision-making by health professionals on the choice and administration of a drug product for an individual patient. This is considered to be the 'practice of medicine' which is a provincial mandate.

Although risk communication to the public and healthcare providers using safety warnings is one of Heath Canada's most important pharmacovigilance strategies, there is a lack of evidence on its effectiveness in changing drug prescribing behaviour or drug use among the public. Research on these issues has shown mixed results. A Health Canada public opinion study that involved a representative sample of 551 physicians, pharmacists, dentists, nurses and naturopaths found that 25% of physicians were aware of safety advisories but only 5% adjusted their prescribing in response to the warnings (235). Another survey by Health Canada of 1,108 Canadian health professionals that examined their responses to adverse drug reactions found that 30% were familiar with health advisories and warnings by Health Canada in the past 12 months; 17% of the physicians said they had used this information in their clinical practice but how this information impacted on their practices was unclear (236).

Dusetzina et al. (237) completed a systematic review that examined the impact of FDA warnings on laboratory or clinical monitoring, decreased medication use and decreased use among subgroup populations. Sixteen drugs and drug classes were included in the review. The authors found that there was no evidence that FDA warnings had an impact on clinical and laboratory monitoring. Conclusions were mixed in terms of warnings reducing drug use in general or in sub-group populations. The authors concluded that risk communication messages appear to be most effective when reinforced over time.

Another systematic review, conducted by Piening et al. (238) found that warnings can have some impact on clinical practice but firm conclusions are difficult to draw. The interpretation of results was complicated because of the small number of drug groups evaluated in the review, deficiencies in the design of studies that were included and inconsistencies in the types of outcomes measured

including the adequate measurement of both intended and unintended outcomes. Unintended outcomes could include patients switching to another drug in the same class or, in the case of warnings about birth control pills, increased rates of abortions. The studies included in the results also did not sufficiently assess confounding factors such as the effect of media coverage on specific drugs which may have affected the response to warnings.

A Canadian study by Friesen at al. (239) examined the impact of cardiac warnings on the prescribing of citalopram, a commonly used anti-depressant. Citalopram is similar to domperidone in that it is associated with dose-dependent prolongation of the QT-interval. Heath Canada warnings issued in October 2011 and January 2012 recommended label changes to citalopram which focused on reducing dose levels and the avoidance of concurrent prescribing of other drugs that affect the QT-interval. These recommendations were similar in general content to those in the 2012 and 2015 Health Canada warnings about domperidone. This quasi-experimental interrupted time-series study examined citalopram prescribing data for all users 18 years and older living in Manitoba from 1999 to 2014.

The results of this study showed that the number of citalopram users rose continuously throughout the entire study period suggesting that the utilization of the drug did not appear to be affected by the warnings. There was a drop in the level of high dose prescriptions in some age groups but the warnings also appeared to have had no impact on the co-prescribing of other QT-prolonging drugs. The study concluded that passive "educational regulatory drug warnings" may lead to simple prescribing changes such as reduced dose levels, but more complex changes, such as reducing the prescribing of interacting drugs that could affect the QT-interval, likely require more robust interventions.

Kesselheim et al. (240) suggest that more extensive research needs to be done in order to determine the impact of drug safety communication on prescribers and people using medications. The authors suggest multiple factors could have an impact on the effectiveness of risk communication messages. These include aspects of perception, intent and decision-making. They suggest that more definitive research could include a mixed methods approach that also takes into account the influence of social media on drug safety communication.

5.5.4 New Ministerial Authorities to Address Drug Safety Problems

Bill C-17, The Protecting Canadians from *Unsafe Drugs Act* (*Vanessa's Law*) (204) amended Canada's *Food and Drugs Act* (FDA) (35) to address drug safety through the strengthening of Ministerial powers to regulate therapeutic products and to implement the mandatory collection of ADR reports from Canadian healthcare institutions. This section examines key new Ministerial powers to respond to drug safety issues. The collection of mandatory ADR reports from healthcare institutions is not discussed in my research because it was implemented so recently, December 2019.

Vanessa's Law is named in memory of Vanessa Young, a Canadian teenager, who died in March 2015 as a result of the cardiac effects of Prepulsid (cisapride), which was prescribed for bloating and digestive discomfort. Prepulsid is a QT-prolonging drug which had a history of safety problems related to heart and heart rhythm disorders identified as early as 1992 by the World Health Organization and later by the US FDA which issued warnings to physicians in 1998 and 2000. Patient information for Prepulsid said that the drug was contraindicated for those with eating disorders, low levels of potassium, calcium and magnesium, for those who had experienced low levels of water in the body and persistent vomiting, all conditions that Young was experiencing when she was prescribed the drug.

None of Vanessa Young's healthcare providers warned the family about the cardiac risks associated with the drug. Health Canada first warned healthcare professionals about the drug in March 2000 but the drug was not withdrawn from the market in Canada by the MAH until several months after the US withdrew the drug (241).

Drugs are usually withdrawn as a result of negotiations between the MAH and Health Canada (242). *Vanessa's Law* includes new regulatory actions that can be taken by the Minister of Health in response to drug safety problems that may present a serious risk to human health, including the ability to withdraw unsafe drugs without negotiating with a MAH. This section discusses several of these new powers and explores their potential applicability to off-label prescribing.

Description, Objectives and Target Group of the Policy

Four new ministerial powers in *Vanessa's Law* to address drug safety are discussed in this section (204). These powers allow for the Minister of Health to order the MAH to take action when the potential risk of a drug to the health of Canadians is identified. Previously, the Minister was required to negotiate with the MAH to undertake regulatory actions such as changing the product label or withdrawing the drug from the market. The specific new ministerial powers discussed in this section are:

i. Section 21.31- not yet in force: Subject to the regulations, the Minister may order the holder of a therapeutic product authorization to conduct an assessment of the therapeutic product to which the authorization relates and provide the Minister with the results of the assessment.
ii. Section 21.32 - not yet in force: Subject to the regulations, the Minister may, for the purpose of obtaining additional information about the therapeutic product's effects on health or safety, order the holder of a therapeutic product authorization to (a) compile information, conduct tests or studies or monitor experience in respect of the therapeutic product; and (b) provide the Minister with the information or the results of the tests, studies or monitoring.

iii. Section 21.2- in force: The Minister may, if he or she believes that doing so is necessary to prevent injury to health, order the holder of a therapeutic product authorization that authorizes the import or sale of a therapeutic product to modify the product's label or to modify or replace its package.
iv. Section 21.3 (1) - in force: If the Minister believes that a therapeutic product presents a serious or imminent risk of injury to health, he or she may order a person who sells the product to (a) recall the product; or (b) send the product, or cause it to be sent, to a place specified in that order.

Health Canada's guide to these new authorities (243) was used to help interpret the meaning and scope of these amendments and to explore their potential applicability to off-label uses when a risk of injury to health is detected. This document is being used as a basis for future operational tools.

Does This Policy Address Off-label Prescribing?

The language of the amendments in *Vanessa's Law* that describes the new Ministerial authorities refers to the holders of a product authorization and, in some cases, to the drug product to which the authorization relates. It is unclear whether this language narrows the application of the amendments to approved indications. For example, Section 21.2 provides the authority to the Minister of Health to order a label change or package modification if s/he believes that doing so is necessary to prevent injury to health. The order is made to the market authorization holder that has received authorization for the sale of a therapeutic product. This language might be interpreted to include both approved and unapproved uses but this could not be verified with Health Canada.

Health Canada's information on these new authorities (243) indicates that safety concerns leading to the order for a label change are related to the therapeutic product and limitations of the product label in describing these new safety risks and may not be restricted to on-label uses. The interpretation within the new authorities is the following:

> 'Health Canada assesses therapeutic products and their labels prior to their being made available for sale in Canada. However, once a product is made available for use in a clinical trial or made available for sale, new information about the harms associated with the use of the therapeutic product may become available that is not adequately reflected on the label' (243: Sect.21: p.2).

The sources of information used to define these harms could be from a wide variety of sources, all of which could apply to off-label uses. They include, 'post market safety signal detection, patient or healthcare institution ADR reporting, information shared from other international regulatory agencies, reports published in scientific literature, or from an inspection performed by Health Canada or another regulator' (243: 21: p.2). Health Canada documents some ADRs related to the off-label uses of some drugs, including domperidone, although these are not collected in a systematic way. It also monitors responses to drug safety issues by other drug regulators such as the EMA.

Section 21.3 of the new powers enables the Minister of Health to recall a product if s/he believes it presents a serious or imminent risk of injury to health. This regulation applies to the person (manufacturer) who sells the therapeutic product which includes both prescription and non-prescription drugs.

The language of Section 21.31 (power to require assessment) and 21.32 (power to require tests and studies), requires the holder of a therapeutic product authorization to provide assessments of the therapeutic product to which the authorization relates. Orders may be issued on the basis of scientific or new evidence.

The amendments in *Vanessa's Law* specify the elements to be used to determine whether the therapeutic product presents a serious risk to human health which is the basis for the Minister's response. The list of elements used to make this determination include the seriousness of the adverse health consequences, changes in the nature or frequency of these consequences, the probability of these consequences on exposure, the vulnerability of the patient population and extent of the population's exposure to the product. All of these considerations could apply to off-label uses.

I discussed my conclusions about off-label uses being subject to the new Ministerial powers with Health Canada officials. They referred me to the Guide to New Authorities described above for direction. Discussions with a Canadian health policy legal expert who has followed the implementation of *Bill C-17* suggested that the amendments may have the potential for including off-label uses where serious risks were identified but this has not been verified by Health Canada.

Summary Comments

Bill C-17 identifies a broad scope of actions Canada's Minister of Health can take if a drug product is considered to pose a serious risk to human health. This section described four of these new powers and discussed their potential applicability to off-label uses. These actions include ordering a manufacturer to make a change in the label, recall a drug or order further tests and assessments of a drug if safety issues are a concern. The language in the Act specifies that this risk is linked to the therapeutic product (drug) itself without clearly specifying that these risks only apply to the approved indications of the drug.

Canadian researchers have identified limitations of the amendments that may affect their application and ability to protect the health of Canadians (244). One issue is Health Canada's lack of a clear definition of terms such as "injury" and "harm" used in the Act. This may mean that, depending on the interpretation of these terms, some drugs with safety risks might not be subject to recall. Another concern is that a drug manufacturer may sue Health Canada for damages if a market authorization is suspended or a drug recalled. This may lead to the Minister's reluctance to invoke these powers unless s/he is exempted from liability. In fact, up to now, none of the new Ministerial powers have been used. Health Canada officials described these powers as having limited application

and being used only in narrowly prescribed circumstances. I was not able to determine whether or how these circumstances have been defined (Personal correspondence, MHPD, March 16, 2019).

5.6 Summary of Findings from the Policy Analysis

Section 5.0 reports the results of a review of Health Canada administrative policy, policy-related documents and governing Acts and regulations in order to determine whether and to what degree the policies that address drug safety issues could apply to off-label indications and if, not, where limitations and gaps exist in response to off-label uses.

Four sources of information were used to identify and analyze Health Canada policies: a search of the grey and academic literature, a review of policy documents on Health Canada's website, discussions with officials from the Marketed Health Products Directorate and with Canadian and legal experts familiar with Health Canada prescription drug policies. Components of four policy areas were reviewed in this section. They included policies related to drug approval processes, post-market surveillance, risk communication and new regulatory powers given to the minister under amendments to the *Food and Drugs Act*.

The analysis found that off-label uses are not specifically addressed by policies in any of these areas. At the same time, there is some acknowledgement by Health Canada that OLU is a factor in drug oversight and may be considered on an ad hoc basis, for example within the content of a Product Monograph or in the collection of ADRs. A recent Safety Review of domperidone acknowledged the growing use of the drug to address lactation problems but it was not clear whether any recommendations arising from the report addressed the risks of this use. One change that appeared to arise from the Safety Review was the broadening of language in Health Canada's 2015 Safety Warning (127) to reference all potential uses of the drug although none of these potential uses, for example the off-label use of domperidone to treat LMS, were specified.

The language in the regulatory amendments giving the Minister new powers to regulate the safety of drugs in *Vanessa's Law* appears to have the potential to include off-label uses but this has not been confirmed by Health Canada or through a considered legal interpretation. However, regulatory responses by Health Canada as seen in *Vanessa's Law* such as the Minister of Heath requiring changes to the product label, could only apply if off-label drug uses were systematically identified and tracked through ADR reporting and then analyzed using signal assessment which is currently not the case. My analysis of policies related to off-label prescribing in Canada determined that, although the practice is common (2, 3), it is not systematically acknowledged, tracked or regulated by Health Canada.

6.0 RESEARCH CONCLUSIONS

6.1 Focus of the Concluding Chapter

The focus of this chapter is to synthesize the conclusions from my research by integrating the results of the Midwives' and Physicians' Surveys, interviews with mothers who have used domperidone to treat LMS and the analysis of Heath Canada's policies related to off-label prescribing in order to address my central research question.

My research question was to identify the key clinician, patient, socio-cultural and policy factors that appear to be associated with the increasing off-label use of domperidone to treat low milk supply in British Columbia. I chose domperidone as a case study of off-label prescribing in order better examine the concrete influences on off-label prescribing.

I used a socio-ecological model (SEM) with multiple levels to provide a conceptual framework for my analysis because it incorporates different levels of influence and actors that individually and in combination can play a part in influencing health-related behaviours such as off-label prescribing (Table 2). The key conclusions discussed in this chapter are categorized by SEM levels related to the following factors: clinician, patient, community, institutional, socio-cultural and the policy and enabling environment. I combined conclusions relating to the community and institutional levels because they frequently overlap.

This chapter also includes a discussion of the strengths and limitations of the research as well as recommendations for further research and improvements in Health Canada's policies and clinical practices relevant to off-label prescribing and drug safety.

6.2 Conclusions Related to Drivers in the SEM

Section 6.2 reports the conclusions related to the specific drivers of the off-label use of domperidone as they are located in the distinctive levels of the SEM I developed as the conceptual framework for my research. Drivers at each level are discussed separately.

6.2.1 Conclusions Related to Clinicians

- Domperidone appears to be frequently used by healthcare providers to treat LMS

Although my sample population of clinicians wasn't representative, the majority of physicians and midwives answering the survey were regularly using domperidone to treat LMS. Research from BC indicates that the rates of domperidone prescribing by family physicians to treat LMS have risen significantly between 2002 and 2011 (1). A 2014 Health Canada safety review of domperidone also indicated that domperidone use to treat LMS in Canada is relatively common and is expected to grow (211). However, there is a lack of accessible updated population-based administrative data that indicates the current frequency of off-label domperidone use to treat LMS.

- Physicians who are more comfortable treating breastfeeding issues are more likely to prescribe domperidone than not to prescribe it.

Most family physicians do not receive specialized training to help them address breastfeeding problems. I was interested in whether the degree to which a physician felt comfortable treating breastfeeding issues had any association with their domperidone prescribing. The results of the logistic regression indicated that the higher a physician's comfort level with treating breastfeeding issues, the more likely it was that they would prescribe domperidone. The data suggests that those physicians who are less comfortable treating breastfeeding issues may be more cautious about using domperidone.

- Midwives who had practices in Vancouver or the Lower Mainland were more likely to prescribe domperidone to their patients than those practising in the rest of BC.

None of my other findings explained this result although there may be differences in how practices are organized in smaller population centres. Location of practice was not a factor in the prescribing practices of physicians. No other practice or personal characteristics were associated with domperidone prescribing among midwives or physicians.

- Midwives who had a higher number of patients with LMS on their caseloads were more likely to prescribe domperidone to their patients.
- The approaches clinicians used to diagnose LMS were inconsistent, sometimes lacked a clear evidence base and were sometimes implemented prematurely. These early diagnoses contributed to early technological interventions, including the prescribing of domperidone and the introduction of formula.

The approaches used to diagnose LMS, as described by the mothers, were often inconsistent, lacked clarity and were frequently based on qualitative assumptions rather than evidence-based methods. LMS was often diagnosed very quickly after the birth. Most of the mothers said that they were unable to identify a specific method or process that was used by healthcare providers to diagnose LMS.

Half of the mothers were told that they had LMS within 2 – 4 days after their baby's birth when their babies had not regained their birth weights. However, this is the period of time when mothers are establishing their milk supply and where it would be unlikely for a baby to have regained this weight. One of the most validated methods for measuring milk volume in an infant is the multiple test/retests weighing of the infant over a 24-hour period. None of the mothers who were interviewed had undergone this comprehensive testing.

Over 80% of the midwives and physicians said that they relied on the mother's assessment of her baby's behaviour to indicate there was a problem with milk supply. Physicians also relied on the mother's reports of having insufficient milk to diagnose LMS. The research literature suggests that

mothers' reports of insufficient milk could be influenced by a mother's lack of knowledge of the process of lactation, her lack of familiarity with changes to the breast after birth or by a misinterpretation of a baby's postpartum behaviour (74, 78, 82, 83). Several mothers believed that the fussiness, sleepiness or frequent night feedings of their babies meant they might be hungry because they weren't getting enough milk.

In a systematic review of breastfeeding self-efficacy, Mannion and Mansell (80) found that maternal perception of insufficient milk production is almost never validated by the systematic measurement of milk volume but is a prime influence in maternal decision-making to supplement with formula, discontinue breastfeeding or use other products that stimulate milk supply.

The concern about when and how LMS is diagnosed is important because, among the mothers interviewed, the diagnosis of LMS was the "gateway" for the introduction of domperidone and other interventions such as formula. The introduction of formula is associated with lowered breastfeeding rates.

Two mothers who had experienced problems with milk supply with their previous babies believed that they would experience it again and obtained prescriptions of domperidone before they gave birth to their subsequent babies.

- Many of the sources of information about domperidone's effectiveness and safety that clinicians found most useful were not highly evidence-based. However, those physicians who considered Cochrane or other independent systematic reviews to be most useful were associated with a lower level of domperidone prescribing.

Overall, physicians and midwives identified lower quality of evidence sources as being "the most useful" in assessing the effectiveness and safety of domperidone. The three sources of evidence that were considered as "most useful" by physicians were advice from colleagues, consensus statements/guidelines by experts and online information. These were cited by over 60% of physicians.

There was more consensus among midwives about the sources of domperidone information that they found to be most useful. Over 70% of the midwives considered consensus statements/ guidelines by experts, information from professional associations or colleges and personal clinical experience with the drug to be the most useful sources of information about the safety and effectiveness of the drug. Ten percent (10%) of the midwives cited pharmaceutical company information as being a useful source of information about domperidone.

The source of information with the highest quality of evidence included on the survey checklist was Cochrane or other independent systematic reviews. Only a third of the physicians identified this information source as being one of the most useful. However, results from the logistic regression indicated that physicians who cited Cochrane and other systematic reviews to be a most useful source

of information prescribed domperidone less frequently to patients on their caseloads who had LMS. This was the only source of information that was significantly associated with prescribing levels.

Consensus statements on domperidone were cited by a high percentage of clinicians as a most useful source of information. Dr. Jack Newman is a co-author of the widely distributed 'Consensus Statement on the Use of Domperidone to Support Lactation' which was endorsed by a number of breastfeeding researchers (126). This statement suggests that the cardiac risks of domperidone are mostly associated with the elderly and that high doses of domperidone may be necessary to successfully treat LMS.

- Recommended medical assessments for patients being prescribed domperidone were not undertaken regularly by all clinicians. Results from the mothers' interviews also indicated that these medical assessments were not consistently carried out.

Just over 80% (120/146) of the physicians regularly assessed a patient's personal and cardiac history and use of concomitant QT-prolonging drugs (120/147). Almost all the midwives, (96.5% or 56/58), regularly reviewed the cardiac history of the patient and her family and over 85% (50/58) said they reviewed the use of other QT-prolonging drugs. The ordering of ECGs was much lower in most groups; 6.9% (4/58) of midwives and 14.5% (21/145) of physicians ordered an ECG frequently or most of the time.

Half of the mothers who were interviewed said that they did not remember receiving any type of assessment by their healthcare provider prior to receiving domperidone. A third of the mothers said that they were asked about their personal or family cardiac history. Only two of the eighteen mothers said that she had been asked about other prescription drugs she was taking. One mother had received an ECG; she was being prescribed five times the daily dose of domperidone recommended by Health Canada.

The assessment of whether a patient is using other QT-prolonging drugs is important because the use of concomitant QT-prolonging drugs has a cumulative effect on cardiac risks. There is a growing list of drugs that have this potential and some are commonly used. The importance of including this type of patient assessment has been emphasized in the most recent Health Canada warning on domperidone (170).

- The majority of clinicians recommended doses of domperidone over the safety guidelines advised by Health Canada. There is a lack of strong research evidence that supports the use of high doses of domperidone as an effective way of increasing milk supply.

Health Canada and the European Medicines Agency recommend a maximum daily dose of domperidone of 30 mg/day. Only 27.7% (13/47) of the midwives and 39.8% (49/123) of physicians recommended doses within these guidelines. The majority of midwives (57.4% or 27/47) and 30 (1%)

37/123) of the physicians recommended doses of 80 mg/day or more, almost three times the dose recommended by health regulators.

The results of the logistic regression found that physicians who recommended doses of domperidone above the guidelines prescribed domperidone to a higher percentage of patients with LMS on their caseloads.

Only three of the eighteen mothers said that they were prescribed doses within the guidelines; half used doses of 80 mg/day or more. Several of the mothers were warned by pharmacists of the risk of the doses they were prescribed (over 100 mg/day). These mothers stated that they believed that high doses of domperidone were the most effective for increasing their milk supply.

There is a lack of high-quality research evidence indicating that high doses of domperidone are significantly more effective at increasing breastmilk supply. Only two RCTs carried out by Knoppert et al. (133) and Wan et al. (134) examined the effects of different dose levels of domperidone (30 mg and 60 mg/day) on milk volume. Both studies had a small number of participants and were of short duration, meaning that that long-term impacts of domperidone on breastfeeding were not measured. Furthermore, these studies showed no significant increase in milk volume by dose level.

- Most clinicians were aware that using domperidone to treat LMS is an off-label use although 10% of the physicians expressed uncertainty about the drug's approval status. A third of the mothers expressed concerns about the safety of a drug that was being prescribed off-label.

Over 90% of the midwives (51/55) and physicians (135/143) were aware that using domperidone to treat LMS was an off-label use. However, when all the physicians were included, 10% (16/159) were uncertain about domperidone's approval status.

In a national US study, Chen et al. (22) found that 40-50% of physicians had trouble identifying whether commonly prescribed drugs were on- or off-label. The authors concluded that if a physician believes a drug has been approved when it has not, they may overestimate the degree to which the drug is safe or effective.

Two-thirds of the mothers reported that they were aware that domperidone had not been approved to treat LMS. A third of the mothers expressed concerns about using an off-label drug and said that more research on the drug's safety as a treatment for LMS should be considered. Clinician awareness of the off-label status of domperidone was not associated with any prescribing patterns or level of use of domperidone.

- The majority of clinicians were aware that Health Canada has issued safety advisories on domperidone. However, most felt that the warnings were not applicable to domperidone when it is being used to treat LMS. The advisories issued by Health Canada do not specifically reference off-label uses which may contribute to clinicians not seeing them as relevant.

All of the midwives were aware of one or more advisories issued by Health Canada on the safety of domperidone. These advisories focused on the potential cardiac risks of the drug, specific risk variables, approaches to use when assessing risks, including the need for specific types of patient assessments. The advisories also included guidelines for safe domperidone dose levels and the maximum duration of use. However, almost 70% (39/56) of the midwives felt that the advisories had no or limited applicability to domperidone when it was used to treat LMS. Eighty-six percent (86%) (137/159) of the physicians were also aware of the advisories with 67% (105/156) believing they had limited or no applicability.

Although Health Canada advisories are posted online, none of the mothers had seen or heard about them. Half of the mothers said they didn't know much about domperidone before they used it; most of the others said that they did preliminary research prior to taking it, frequently using online sources of information.

I was unable to determine why clinicians considered the advisories to have low applicability to domperidone when it is used to treat LMS. The advisories are focused on the approved uses of domperidone, primarily its use as a treatment for gastric motility problems among those with Parkinson's Disease, rather than on off-label uses. This focus may mean that clinicians believe the risks of domperidone do not apply to treating LMS or to younger women who are breastfeeding. However, the latest advisory on domperidone (170) stated that it applied to all conditions even though none of these conditions were specified.

Several mothers said that when they raised concerns about using domperidone with their physicians they were told that any cardiac risks applied only to elderly women. It is not clear how widely this view is held by clinicians. Among the clinicians the Consensus Statement on the Use of Domperidone to Support Lactation (126) was one of the more frequently used resources on domperidone's safety and efficacy. This document stated that the cardiac risks of domperidone applied primarily to elderly women.

My findings could also indicate a problem with the impacts of drug warnings in general. Research suggests warnings issued by health regulators have mixed results (237-239). Many drug advisories appear to have delayed or no effects, have impacts only in certain circumstances, or can sometimes lead to unintended consequences.

- The vast majority of clinicians believed that domperidone posed no or minimal risks to patients or their infants. There was a higher level of uncertainty about the risks of domperidone to infants among clinicians. Physicians who assess domperidone's risks to babies as more significant tend to prescribe domperidone less frequently.

Despite the cardiac and other risks associated with domperidone use, approximately 80% of midwives and physicians believed that domperidone posed no or minimal risks to breastfeeding mothers. The estimate of domperidone's risks to babies was even lower: 94.2% (129/137) of physicians and 100% (47/47) of midwives felt that the drug posed no significant or minimal risks to infants. The results of the logistic regression indicated that when physicians assess the potential risks of domperidone to babies to be significant, the less likely they are to prescribe domperidone to patients they are treating for LMS.

There was a higher level of uncertainty about the level of domperidone's risks to babies among the clinicians. When all answers to the question about risks to babies were considered, 13.3% (21/158) of the physicians and 15.8% (9/57) of the midwives expressed uncertainty about the risks.

None of the mothers who had taken domperidone when they were breastfeeding felt that their babies had experienced ADRs from domperidone received through breast milk. Just over half of the mothers identified a range of potential ADRs they personally experienced. The most frequent ADRs mentioned were weight gain, stomach and bowel problems and severe and lasting headaches.

Two mothers experienced serious withdrawal effects when they tried to reduce the dose of domperidone. These effects were similar to those experienced by individuals withdrawing from neuroleptics such as an upsurge in feelings of despair and anxiety as well as having symptoms of akathisia. Domperidone is in the neuroleptic family and similar withdrawal effects have been described in the case study literature (143,144).

6.2.2 Conclusions Related to Patients

- Most mothers who had used domperidone to treat LMS had limited family support or modelling to support their breastfeeding.

A third of the mothers who were interviewed had a close family member, such as a mother or sister, who had breastfed. Only two of eighteen mothers said that they had strong social support and personal advocacy for breastfeeding from a partner. Arora et al. (198) and Kessler et al. (199) found that support from a partner or other family members helped to encourage a mother's breastfeeding. Rempel et al. (200) found that a father's perception of his support to breastfeeding predicted breastfeeding success and satisfaction for men and women, but also appeared to be associated with shorter breastfeeding duration. This study raised questions about the types of behaviours from fathers that were considered supportive of breastfeeding by mothers.

- Mothers routinely used non-pharmacologic galactogogues to try to increase milk supply.

Over half of the mothers had used from two to nine non-pharmacologic galactogogues to try to increase their milk supply. The majority of the mothers later assessed these as being ineffective. Several physicians who were surveyed said that some of their patients were desperate to try anything to increase their milk supply. Some mothers also said that their use of non-pharmacologic galactogogues reflected this desperation.

- Patients often initiated discussions with clinicians about using domperidone to treat LMS.

Results from the clinician surveys indicated that, in some cases, patient wishes may have influenced clinicians to prescribe domperidone or to prescribe doses above the recommended guidelines. Just over 14% (8/56) of the midwives and 27.2% (43/158) of the physicians said their patients had initiated the discussion of using domperidone at least 50% of the time. Several of the mothers who were interviewed said they convinced their physicians to maintain the higher daily dose levels of domperidone that they were prescribed even though a pharmacist had raised concerns about the safety of these doses. In both these cases, the prescribed doses of domperidone were over 80 mg/day.

- Clinicians and mothers had differing views on the impact of domperidone on breastmilk supply. Although clinicians were more positive about the drug's effectiveness in terms of promoting breastfeeding without supplementation, how they assessed this outcome and whether it was long-lasting was unclear. The majority of the mothers assessed domperidone as being unhelpful or were ambivalent about its effects on their milk supply.

A majority of physicians and half of the midwives said that at least a half of their patients were able to exclusively breastfeed without using formula or donor milk after using domperidone. The survey did not ask clinicians how and when in the postpartum period they measured these outcomes so this finding should be interpreted with caution.

The majority of the mothers were either uncertain about domperidone's effectiveness or felt it had not helped increase their milk supply. A third of the mothers felt that the drug had helped increase their milk supply.

- Domperidone use had unintended consequences for many of the mothers.

Prescribing domperidone led to the early introduction of formula for the majority of the mothers and the need for them to undertake time-consuming pumping, formula/bottle-feeding and breastfeeding schedules. At least a third of the mothers said that they found these demands stressful, overwhelming and exhausting with each feeding arrangement taking several hours and sometimes being repeated about eight times a day. One mother said that this regimen contributed to her experiencing a serious postpartum depression.

6.2.3 Conclusions Related to Community and Institutional Factors

- Key influencers may be a factor in promoting the use of domperidone to treat LMS and, in some cases, supporting the use of doses over recommended safety guidelines.

Just under a third of the mothers who used doses of domperidone that were well over the recommended guidelines said they were influenced by the recommendations of Dr. Jack Newman, a physician and breastfeeding advisor who runs a breastfeeding support site.(172). He is a contributor to the 'Consensus Statement on the Use of Domperidone to Support Lactation' (126) which supports the use of domperidone to treat LMS and the use of high doses of the drug if considered to be necessary. Consensus statements were rated as one of the most useful sources of information about domperidone's safety and efficacy by both the physicians and midwives so they appear to be influential. However, they are not considered to be a strong evidence-based source of research information.

- Early hospital discharge affected the establishment of a mother's early milk supply and led to poor continuity of care. A majority of the mothers also said that they received contradictory and sometimes upsetting advice about breastfeeding from multiple healthcare providers.

All but one of the mothers gave birth in a hospital. More than half of the mothers were discharged within 24 hours of giving birth. At the point of discharge, mothers were still recovering from the birth, babies were still losing weight and the mother's milk supply was not yet established. Early discharge also took place before women had received sufficient instruction in breastfeeding (for example, correct latching positions of the baby at the breast) and before most babies started showing the signs of jaundice. Over half of the mothers said jaundice became a concern when they arrived home and many mothers found this distressing.

Almost 40% of the mothers said that they had early problems with establishing the baby's latch to the breast and how to deal with their baby's sleepiness or lack of interest in the breast which they sometimes interpreted as hunger resulting from a lack of milk supply. Leaving the hospital so early also meant that many mothers also experienced a gap in access to healthcare providers in the transition period between the hospital and the community when breastfeeding challenges like these were most acute.

Almost all of the mothers had multiple (from two to nine) healthcare providers in the hospital and community who provided breastfeeding advice to them. These included hospital nurses and hospital-based lactation consultants, midwives, physicians, public health nurses, community-based lactation consultants and other healthcare providers such as pharmacists, dentists and chiropractors in a small number of cases. Two-thirds of the women said they also eventually hired a fee-based private lactation consultant. The hiring of private, fee-based breastfeeding assistance, which some women

found difficult to afford, reflects a lack of accessible community support for new mothers and their babies.

Most of the mothers said that most of the healthcare providers provided a high quality of care both at the hospital and in the community. However, the fragmentation of care meant that many of the mothers said they received contradictory advice about breastfeeding and the status of their milk supply. Ten of the 18 mothers said they were confused about the contradictory advice they received about whether to use formula, how much and how often to pump milk, how much infants needed to eat, and the timing of interventions to increase milk supply such as pumping. Sometimes contradictory advice was given to mothers about breastfeeding by healthcare providers who were part of the staff at the same hospital or who worked in the same clinical practice.

A third of the mothers said that they felt pressured to use formula. Some were told that they were starving their babies. Several others were told, a few days postpartum, that they would never be able to breastfeed. Another mother was told she should have a very large milk supply two days after birth. These comments appear to reflect a lack of understanding, on the part of some healthcare providers, of best practices in relation to lactation, infant development and the stressors involved in parental/family transition.

These comments also ignited fears among many of the mothers that their situation might be hopeless, that LMS was a permanent condition, that they were potentially harming their babies by wanting to continue to breastfeed and that they were personal failures.

- There was a lack of consistent pre-natal and post-natal breastfeeding education available to mothers that addressed challenges that could arise during breastfeeding.

All of the mothers involved in the research had accessed a variety of different types of information about breastfeeding before and after giving birth. A third of the mothers attended prenatal or breastfeeding support classes or talked with a lactation consultant about breastfeeding before giving birth. Almost half of the women connected with a local breastfeeding drop-in group, usually sponsored by public health or through La Leche League, after their babies were born, although most said they did not attend these groups regularly. Eighty percent (80%) accessed online sources of information such as breastfeeding groups on Facebook, including one for breastfeeding mothers using domperidone. A third of the mothers followed Dr. Jack Newman's website on breastfeeding. Two-thirds of the mothers eventually hired a lactation consultant to help them with LMS and other problems.

There was a concern expressed by half of the mothers about the breastfeeding information they felt they lacked. Many said that they would have liked to hear more about the challenges that could arise during breastfeeding. One of the mothers stated that in her prenatal class there was more of a focus on the challenges that could arise during the birthing process than might be encountered during breastfeeding.

Findings from the research literature indicate the importance of breastfeeding education as a way of building a mother's breastfeeding self-efficacy (BSE) and confidence. A high level of BSE has been associated with an increase in breastfeeding duration and, in some cases, a decrease in the maternal perceptions of LMS (77). Results of systematic reviews by Galipeau et al. (92) and Brockway et al. (90) found that educational interventions that spanned the pre- and post-natal period were the most effective at increasing breastfeeding self-efficacy as were interventions based on education that involved multiple contacts with mothers.

6.2.4 Conclusions Related to Socio-Cultural Factors

- The use of domperidone to treat LMS reflects aspects of the medicalization of breastfeeding. The medical management of breastfeeding does not create an environment that is conducive to enhancing women's' confidence in their ability to breastfeed especially in the first few months postpartum.

Medicalization refers to the process by which some aspects of human life are considered as medical problems, whereas previously they were not considered as pathological (106). Defining LMS as a pathology or disorder is an aspect of medicalization. Although, for a minority of women, physiological conditions are the major cause of problems with milk supply, the results of my research indicate that socio-cultural factors and beliefs helped drive the diagnosis and treatment of LMS which led to the use of domperidone. These factors include the over and early diagnosis of the condition before a mother's milk supply had been established, clinical practices which led to early medical interventions with domperidone, formula and pumping, the exaggeration of the over-all risk of LMS to most breastfeeding mothers and the reliance on the medical management of a condition that was once within the domain of a woman's experience and informed by her own knowledge and relationships with other women.

Moynihan et al. (115) describe over-diagnosis as a major feature of medicalization. Over-diagnosis expands the threshold for defining a health problem so that people with milder problems and smaller risks are included in the diagnosis which then leads to the overtreatment of many. Over-diagnosis is supported by cultural beliefs that early detection and treatment is the optimum approach.

An increase in testing and measurement helps drive over-diagnosis. My research found that few mothers had their milk supply assessed using validated approaches although their milk volume was constantly observed after milk pumping. This type of micro-management increased mothers' level of stress.

The management of LMS by medical experts is another hallmark of the medicalization of breastfeeding. Torres (103) notes that there is an expectation by mothers that they should consult medical specialists for help with breastfeeding concerns although many of these problems were formerly addressed by family members or peers who had breastfed. The trend towards using

specialist managers reflects the growth of 'scientific motherhood' which appeared in the United States in the 20th Century. This movement stressed that women needed the scientific and medical advice of experts in order to raise healthy children. The adoption of this approach corresponded with a drop in breastfeeding rates at the time.

An antidote to the medical management of breastfeeding is the use of peer-to-peer breastfeeding support which is built on and validates women's' experiences. However, most of the mothers involved in the study did not use these services to any great extent and instead relied more on online information. Mothers seeing examples of successful breastfeeding also provides support for having a rewarding breastfeeding experience. Most of the mothers participating in the interviews did not have family members who modelled breastfeeding and many said that they lacked meaningful support from their partners.

Another force driving the medicalization of breastfeeding is the reliance on the use of technologies and information, rather than on behavioural or social supports, which have been used in the past to support breastfeeding. The use of domperidone, itself a technology, appeared to be a gateway to the use of other technologies used by the mothers such as the early introduction of infant formula, breast pumps, nipple shields and feeding syringes. Many of the mothers participating in the interviews had multiple breast pumps of different sizes and capacity.

Torres (103) notes that the measurement of breast milk production, using scales that measure tiny increments of milk, contributes to the medicalization of breastfeeding. Breast pumps also enable healthcare providers and mothers to see, quantify and track how much milk is being produced and to set goals for milk production which some mothers found to be stressful. Seeing and measuring small increments of breastmilk can reinforce women's anxiety about having insufficient milk and objectifies breastmilk as a "medicinal product" with nutritional elements rather than fully reflecting breastfeeding as a dynamic relationship between a mother and her baby. Some of the mothers in the research said that they found these measuring sessions reinforced their sense of failure.

The author notes that the medical management of breastfeeding can lead to women feeling detached from their own bodies which can undermine their confidence in their ability to produce milk. Mothers' reports of high stress levels, a lack of confidence, and disappointment in their own bodies were common themes expressed by the mothers who were interviewed. All of the mothers involved in the interviews were deeply committed to breastfeeding and wanted it to succeed. However, for fifteen of the eighteen mothers in the first few months postpartum, breastfeeding was frequently a high stress endeavour characterized by trying multiple approaches to increase milk supply including the use of domperidone, consulting with multiple healthcare providers, struggling with inconsistent medical advice, trying to interpret baby signals and, for many, undertaking time-consuming pumping, bottle-feeding and breastfeeding schedules that they found to be exhausting and stressful.

When individual mothers were asked to describe how they experienced the first few weeks or months of breastfeeding, they used phrases such as 'being beside oneself', 'being upset and exhausted', 'being on a roller-coaster ride', 'feeling heartbroken,' and 'as if they were going to lose their mind'. Several felt that they had failed as mothers and that their bodies had betrayed them. Some worried about whether breastfeeding had been the right thing to do. Almost 40% of the mothers said that discouraging comments from healthcare providers about their milk supply added to their sense of failure.

In summary, although impossible to quantify, the impact of medicalization on the mothers' experiences of breastfeeding appears to have been significant. Early diagnosis and medical interventions, including the medical management of breastfeeding, did not create an environment that was conducive to enhancing mothers' sense of self-efficacy or boosting their confidence in their ability to breastfeed in the first few months postpartum.

6.2.5 Conclusions Related to the Analysis of Health Canada's Policies

- Health Canada does not routinely track, monitor, oversee or regulate off-label prescribing. This lack of regulation is a disservice to Canadian healthcare providers who need comprehensive information about a drug's safety and effectiveness before prescribing. It also exposes the Canadian public to drugs that are potentially harmful and lack strong scientific evidence. The lack of a policy response to off-label prescribing does not meet the standard set by Health Canada which is to protect Canadians and facilitate the safe provision of products such as pharmaceuticals that are vital to the health and well-being of citizens.

Health Canada views the way that prescription drugs are used as part of the practice of medicine which is under provincial jurisdiction. The federal government is therefore reluctant to stray into areas that can be interpreted as interfering in the clinical discretion of physicians. There would also likely be resistance from physicians if their discretionary powers were limited. However, there are many areas under federal jurisdiction where Health Canada has the mandate and the responsibility to monitor, regulate and communicate safety issues associated with off-label prescribing as is now done with approved indications. A clearer and more active policy response to off-label prescribing is essential in order for Health Canada to meet its stated mandate of protecting the health and safety of Canadians.

Policy areas related to off-label prescribing where Health Canada could and should be playing a more proactive and visible role include requiring common off-label uses and their potential harms to be systematically included in drug Product Monographs when post-market data indicating safety problems for a drug used off-label becomes evident. Risk communication messages should also identify common off-label uses and the risks associated with them when the surveillance data indicates these problems. ADR reporting forms should be revised or a process developed to allow for

systematic monitoring, aggregation and analysis of ADRs associated with off-label uses and their inclusion in the process of signal detection to identify safety issues. It is not realistic to expect most reporters of ADRs to identify whether an ADR is associated with an on or off-label use of a drug, but Health Canada could make this link based on information on the drug associated with the ADR and the indication for which it was prescribed. Revisions to the wording of the reporting forms may have to be adjusted to make the collection of this data easy to report or analyze.

Where safety issues with off-label uses are identified, further investigations of these issues by Health Canada, for example, through Safety Reviews, should be undertaken. These reviews should routinely address off-label uses for any drug that have been identified as having a safety problem. The options for remedial actions arising out of these reviews should include those necessary to deal with off-label uses where this is appropriate and should be published without redactions so that the reasoning behind them is transparent. Whether and how recommendations in a Safety Review are acted upon should be disclosed so that Canadians are aware they have been implemented.

Vanessa's Law gives the Minister of Health more discretion to disclose CBI where human health and safety are concerns. The extensive use of labelling publicly relevant information about drug safety and use as CBI in Safety Reviews, including those for domperidone, needs to be addressed. The goals of transparency and public safety cannot be met if a seminal report on a drug's significant safety issues has a large proportion of its content redacted.

Vanessa's Law does not reference off-label prescribing. New powers under this Act, that give the minister the ability to take more concrete actions to protect the health of Canadians when a drug safety problem is identified, are important steps forward. Whether off-label uses are covered under the Act needs to be clarified and, if not, steps need to be taken to ensure this is the case.

Clinicians are not always able to identity when a drug is being used off-label for a particular indication. According to Chen et al. (22) this means that they may overestimate the safety and effectiveness of a particular drug they are prescribing off-label because they assume it has been approved. Although informing patients about off-label uses falls within the practice of medicine, which is a provincial mandate, physicians being able to identify off-label uses and address any gaps in information is an essential foundation for discussing prescribing options with patients. Research indicates that most members of the public do not understand off-label prescribing and are much more cautious about taking a drug when they are informed that the drug is being prescribed off-label (48-50).

Some Canadian researchers (2, 30) have suggested that Electronic Health Records could be modified to include the indication for the drug in the prescription so as to allow the identification of whether a physician is prescribing specific drugs on or off-label. Although this information may not lead to changes in prescribing behaviour, it may be a logical first step in informing physicians systematically about how often and in what circumstances they are prescribing drugs off-label.

Research on drug safety suggests that off-label prescribing needs more, not less scrutiny from healthcare providers because of the lack of evidence for the safety and effectiveness of many off-label uses. In essence, when healthcare providers prescribe a drug off-label they are prescribing a drug that has not been shown to be safe and effective enough to warrant approval by Health Canada. If a new off-label use starts after a drug has gone off-patent the company producing the generic form will not conduct clinical trials to assess the effectiveness of that use. Canadian and American research already indicates that the vast majority off-label uses lack strong scientific evidence.

On a broader level, Health Canada's lack of a comprehensive policy response to off-label prescribing undermines its own regulatory mandate which is to protect Canadians from unsafe and ineffective drugs (245). This allows pharmaceutical companies to tolerate and even encourage off-label use because it is profitable and because they may be able to avoid expensive and time-consuming drug approval processes. Penalties to discourage the illegal promotion of off-label uses have been largely ineffective in the United States (8) and are rarely used in Canada. Off-label prescribing also compromises the principle and expectation that physicians should make prescribing decisions based on a comprehensive assessment of a drug's risks and benefits.

Considering the extent and impacts of unregulated and non-transparent off-label prescribing in Canada, of which domperidone is just one example, why do Health Canada's policies basically ignore off-label prescribing? As noted above, there is reluctance on the part of the federal government to interfere with the provincial authority to regulate the practice. It is likely that physicians themselves would resist any restrictions that would affect their prescribing discretion. Off-label prescribing is common in Canada and can be beneficial when there is a lack of approved drugs for specific conditions or where certain groups such as children, the elderly and those with chronic diseases may lack treatment options because they are not systematically included in clinical trials.

Currently, Health Canada lacks the resources to significantly improve post-market surveillance activities, many of which are relevant to the assessment of safety problems that can arise from off-label uses. Health Canada allocates over three times the personnel and monetary resources into approving drugs through the Therapeutic Products (TPD) and Biologics and Genetic Therapies (BGTD) Directorates than it does into post-market surveillance activities through the Marketed Health Products Directorate (MHPD) (Dr. Joel Lexchin, Personal Communication, August 19 2020). This not only affects the capacity of MHPD to conduct and expand post-market drug surveillance activities that include off-label uses but also reflects an imbalance of power, intent and priorities that exist within Health Canada. Until Health Canada addresses this resource and power imbalance between drug approval and drug monitoring, efforts to improve the safety monitoring of both approved and unapproved drugs will be deficient.

Perhaps the strongest reason for Health Canada's inaction on off-label prescribing lies in the resistance of manufacturers to regulate the practice. According to Marc Rodwin, a professor of law

who writes on ethics and the pharmaceutical industry in the United States, the root of unmanaged off-label drug use lies both with flawed government regulations and the drug industry's strong financial incentives to continue the practice.

> 'Current law prohibits certain off-label marketing practices, yet it does little to remove the direct financial incentives for drug firms to tolerate and even encourage off-label use. The potential to profit handsomely – sometimes to earn billions of dollars - outweighs any potential liability' (206: p.23).

Until these jurisdictional practice issues, resource and power deficiencies at Health Canada and the influence of the pharmaceutical industry are addressed, it is unlikely that off-label prescribing will be effectively regulated by Health Canada. Without Health Canada's involvement in the regulation of off-label prescribing, the health and safety of Canadians will continue to be jeopardized.

6.3 Conclusions Related to the Primary Research Question

My research concluded that multiple factors at the patient, prescriber, institutional, community, socio-cultural and Health Canada policy levels have all helped drive the off-label prescribing of domperidone to treat LMS in BC. While these multiple factors contributed both individually and in combination to the off-label use of domperidone, I was unable to establish the individual weight of different drivers or their most significant interrelationships.

An important contribution of this research is that, in order to understand why off-label prescribing occurs, it is vital to take a multifactorial approach and not just consider the practice primarily as a prescribing issue.

One of the challenges I encountered while doing this research was the difficulty of determining whether domperidone's increasing use to treat LMS in BC (1) had been influenced by its off-label status. Did clinicians take the off-label status of domperidone when used to treat LMS into account before prescribing the drug? Would prescribers have been more cautious about prescribing domperidone to treat LMS if Health Canada's warnings had referenced this off-label use, had stated that female gender as well as age are risk factors, and that risks are dose-related? Some mothers stated that their healthcare providers dismissed their safety concerns about domperidone and told them that the drug's cardiac effects applied only to elderly women. They might have been more cautious about using domperidone if their healthcare providers had provided more comprehensive information about the drug's safety and effectiveness.

Health Canada's lack of regulation of off-label prescribing has likely been one of the most important influences on the increase in off-label prescribing of domperidone in BC. Because of Health Canada's lack of an explicit policy response to off-label prescribing, healthcare providers and the public may not be aware of the potential safety risks or lack of effectiveness of a drug like domperidone when it is being prescribed off-label to treat LMS. The belief that domperidone posed

minimal risks to breastfeeding mothers and their babies and that it appeared to be effective was an opinion of many of the clinicians who participated in the survey.

The results of the logistic regression showed significant associations between some variables and whether or not clinicians prescribed domperidone or used it frequently on their caseloads, but no clear patterns emerged. These variables did not seem to be specifically related to off-label use but to prescribing in general. Physicians who were more comfortable treating breastfeeding problems were more likely to prescribe domperidone which suggests a level of comfort with domperidone's off-label status. Physicians who believed domperidone posed more risk to babies were less likely to prescribe it, but whether their assessment of risk related to its off-label status was unclear. The use of Cochrane and other independent systematic reviews, the highest level of research evidence, was associated with less frequent prescribing of domperidone to mothers with LMS on the physician's caseload. This finding may be linked to physicians having additional concerns about the drug's safety as an unapproved use or could be related to a physician's general practice orientation.

The information sources that clinicians most frequently used to assess domperidone's safety and efficacy were frequently qualitative in nature and not clearly evidence-based. The reliance on some of these information sources indicate that healthcare providers might not be accessing information in the medical research literature indicating that domperidone has not been shown to be effective at significantly increasing a mother's milk supply.

Aronson and Ferner (52), Gazarian et al. 55) and Largent et al. (56) suggest that drugs prescribed off-label require additional scrutiny prior to being prescribed. This includes the consideration of high-quality evidence and focused assessment guidelines to assist in decision-making. Decision-making guidelines recommended by Aronson and Ferner include an assessment of whether the health condition being addressed is severe or life-threatening, whether there are other authorized treatments to manage it and the degree of evidence for the drug's effectiveness. Guidelines also include whether patients have been informed about the risks of the drug and have been able to engage in an informed consent process and the capacity of health regulator to track the drug's adverse events and outcomes in order to monitor the drug's safety.

None of these conditions have been met in the case of domperidone when it is used to treat LMS. LMS is not a life-threatening condition and there are well-established effective non-pharmacologic treatments available to treat it (74,76,81,82,84,85,86,87,90). The evidence that domperidone significantly increases milk supply or that doses of over 30 mg a day are more effective is weak. Health Canada does not systematically collect data on ADRs on any off-label uses, including domperidone when used to treat LMS so that the drug's harmful effects on patients using it to increase their milk supply is lacking.

6.4 Limitations and Strengths of the Research

I developed a SEM to use as the conceptual framework for this research in order to differentiate and discuss the factors affecting domperidone use at the patient, clinician, institutional/ community, socio-cultural and Health Canada policy levels. Although the SEM can help identify factors which may help drive off-label prescribing at different levels, I was unable to measure the comparative "weight" of these factors within and between the levels or determine causality. For example, to what degree do Health Canada's policies on risk communication affect clinicians' views of the risks posed by domperidone and encourage or discourage its off-label prescribing? How do factors related to medicalization, such as the early diagnosis of LMS, affect the confidence of breastfeeding mothers and influence their choice of a pharmaceutical intervention, rather than their relying on longer-term non-pharmacologic methods that increase breastfeeding self-efficacy? From an institutional/community level, how does the fragmentation of care, characterized by early hospital discharge and lack of post-partum support influence mothers' use of domperidone? The degree to which these potential relationships affect the prescribing of domperidone can only be determined by looking at these potential relationships with a narrower research focus.

The survey components of my research were affected by the limitations of the respondent contact methods that were available. Due to privacy provisions of the Midwives Association of BC and the BC Family Practice Divisions, I was unable to send survey invitations directly to clinicians but had to rely on internal postings about the survey distributed by these organizations to their members. I was not able to ascertain whether and how often clinicians saw these internal postings. I was also unable to establish whether certain groups of clinicians, (for example, those who did not prescribe domperidone to treat LMS), selected themselves out of the survey at disproportionate rates. To avoid selection bias, my survey description and invitation stressed that I wanted to include different types of clinician approaches for treating LMS in the research.

Dillman et al. (179) suggest that multiple survey reminders are essential in order to increase the participation rates of online survey participants. All of the Family Practice Regions agreed to post the research information at least twice and the College of Midwives of BC agreed to post the invitation three times. However, since these were internal postings, I was not able to ascertain the degree to which these additional postings took place or whether they were observed by members.

Being unable to clearly ascertain the exact size of my survey populations and the limitations of my contact methods contributed to the fact that I was unable to achieve the target rate of physicians necessary to indicate a representative sample. Because of this I was unable to determine whether my findings could be generalized to family physicians in BC who provide postpartum care. In addition, because my outreach to midwives involved a convenience sample and I could not compare my results with demographic or practice data from larger, more representative provincial organizations, I was also

unable to determine whether the findings from the Midwives' Survey were generalizable to midwives in BC.

Some of the questions on the surveys were based on estimates made by clinicians. These included estimates on the percentage of patients with LMS on their caseloads and the percentage of mothers who were able to exclusively breastfeed without supplementation after using domperidone. Results based on estimates should be interpreted with caution. It is not clear how and when clinicians were able to assess the degree to which domperidone contributed to exclusive breastfeeding. Typically, midwives only provide postpartum services for about six weeks after a baby's birth so their assessments would also be time-limited.

The recruitment of mothers for the qualitative interviews involved sending information about the research to healthcare professionals, breastfeeding groups and public health clinics with a request to notify their clients about the research. Each potential participant who contacted me was vetted to determine if they met the research inclusion criteria. Mothers who met these criteria were invited to participate in the survey on a first come, first served basis. I was unable to establish how representative the experiences of these mothers with domperidone were.

There were multiple challenges related to the policy review component of the research. There were few references to off-label prescribing in the policy documents related to drug approval, ADR collection, safety reports and risk communication or within regulatory documents such as the Food and Drugs Act and Bill C-17. Looking for something that may not exist is challenging and any limitations in my search of Health Canada policy documents were sometimes difficult to ascertain.

Interviews with officials from Health Canada's Health Product Directorate, which were held in order to clarify regulations and policies related to off-label prescribing, lacked specificity and offered little guidance beyond referring me back to the documents on the Health Canada website that I had already considered. Although I identified some minor changes to some of the language used in Health Canada policies that seemed to indicate more focus on the tracking of off-label uses, I was unable to clarify the meaning or intent of these changes with officials.

There was a lack of transparency on the part of Health Canada on how off-label prescribing was being managed, for example, on whether and how signal detection is used for off-label drug uses as well as lengthy delays in acquiring the Health Canada Safety Reports on domperidone, although these are public documents. There were also months of delays between my submission of questions to Health Canada and their replies. In some cases, I received no responses to my questions. In another case, the Health Canada person assigned to answer my questions was unwilling to engage and told me that I had no right to take up her time.

My research design was originally based on an analysis of the data using the dependent variable of clinicians prescribing or not prescribing domperidone to patients on their caseload with

LMS. However, there were insufficient numbers of midwives who did not use domperidone to treat patients with LMS to constitute a group for analysis. This necessitated the post-hoc selection of another dependent variable based on an existing survey question for the analysis of the midwives' survey and for some of the physicians' survey data. For the new dependent variable, I chose a question on the survey that asked clinicians to estimate the broad percentage of patients on their caseloads with LMS who they treated with domperidone. I considered this a surrogate marker which best represented the level of commitment to, interest in and use of domperidone to treat LMS. Using this data as my dependent variable necessitated using question and answer categories that were not originally designed for this purpose. The category I used to indicate clinicians' lower interest in or commitment to domperidone use were those who prescribed domperidone to less than 25% of the patients on their caseloads. I considered this approach to have face validity. It was discussed with a statistician, another researcher and was approved by my primary research supervisor.

One of the strengths of my research was its interdisciplinary approach and the use of multiple but complementary methodologies. Looking at the range of potential contributors to the off-label prescribing of domperidone at the patient, clinician, community, institutional and policy environment levels provided the most comprehensive approach to addressing my research question.

The value of this multi-level approach was recently reaffirmed in a comprehensive study of the off-label use of medicinal products in all the countries of the European Union (9). The objective of this study was to provide information about the regulatory, healthcare system, professional and patient drivers of off-label prescribing because of the perceived risks and economic impacts of unregulated off-label prescribing in the European Union. The study concluded that off-label prescribing is complex, is driven by a combination of factors, that the relative contribution and interaction of drivers is unknown but that a multifactorial research approach to understanding the practice is required.

The authors noted that although policy options affect most of the drivers of off-label prescribing and the drivers may vary, a lack of understanding of these drivers and how they interact, 'hampers a rational choice in whether or not, and what, new (medication) options to embrace' (9: p.104). The results of my research will contribute to the limited literature on this subject and is, to my knowledge, one of the few studies that has been conducted on off-label prescribing in Canada.

My research also included the voices of mothers who have experienced LMS and have used domperidone to treat it. Since LMS is one of the main reasons why mothers stop breastfeeding before they intend to, and often before all health benefits can be achieved, the importance of understanding mothers' experiences with LMS is essential from a health promotion perspective.

6.5 Recommendations Arising from the Research

This section presents recommendations for future research and improved clinical and policy approaches to improve the safety and effectiveness of off-label prescribing and the treatment of LMS.

A policy response to off-label prescribing is critical because, as concluded by Weda et al. (9), in a study of off-label prescribing in the European Union, policy options affected most of the other drivers of off-label prescribing in Europe. In my research, the policy or enabling environment provided an important context for understanding and potentially improving the safety and effectiveness of off-label prescribing.

6.5.1 Recommendations for Future Research Facilitated by Health Canada

i. ADR tracking and Signal Detection

ADR tracking and signal detection are the foundation of the post-market surveillance of prescription drugs in Canada and a key element for ensuring drug safety. Health Canada does not routinely identify or track off-label uses of prescription drugs in order to identify signals that indicate a potential safety problem. Some information about off-label indications is collected on ADR reports in an ad hoc way and is recorded on the Canada Vigilance database. However, this is not a requirement, suggesting that information about harms is unreliable. The ability of Health Canada to routinely collect and analyze ADRS from off-label uses is affected by the lack of resources to address post-market surveillance within the Marketed Health Products Directorate as noted in Section 6.2.5.

Recommendation: That Health Canada undertake a pilot project to determine the degree to which ADR reports indicate off-label uses using examples such as domperidone to treat LMS, how reporting forms could be improved to routinely meet this requirement and how Health Canada could most effectively link the drug's approved indication and drug identified with the ADR to determine off-label use. An improvement in the quality and comprehensiveness of ADR reporting would lead to more reliable data in Health Canada's Vigilance database. This would enable the Minister of Health to monitor safety problems related to common off-label uses in a systematic way and address them, if required. This improvement would require that Health Canada allocate more personnel and monetary resources to the MHPD to improve this key component of post-market surveillance.

ii. Research Related to the Off-label Prescribing of Domperidone to Treat LMS

Only one study has been conducted in Canada on the prevalence of off-label domperidone use to treat LMS. This study, conducted in BC (1), found that there were increasing rates of the off-label use of domperidone to treat LMS between 2002 and 2011. Dose levels and duration of use also increased during this period. However, these findings have not been updated to determine whether these trends have continued. There has been no national research on the prevalence of off-label domperidone use in other provinces.

Recommendation: That Health Canada facilitate the funding of a national study to determine the prevalence of the off-label prescribing of domperidone to treat LMS. This research should also update the findings from the BC survey to see if the increase in the off-label use of domperidone in this

province has continued. It is recommended that this study include an interrupted time series design component to assess the impact of the 2015 Health Canada warnings on domperidone prescribing behaviour.

iii. Research on the Cardiac Outcomes of Domperidone in Women of Reproductive Age

Only one Canadian study (162) has examined the cardiac outcomes specifically in women of reproductive age who used domperidone to treat LMS. This retrospective population-based cohort study looked at all women with a live birth in BC between January 2002 and 31 December 2011 in order to estimate the rate of hospitalization for VA (ventricular arrythmias) among women who were or were not exposed to domperidone. The study found that there were 21 hospitalizations for VA during the postpartum period and that the risk of VA was approximately double among those exposed to domperidone although this relationship was not statistically significant. This study lacked power due to the small number of identified outcomes, an inability to conduct dose-response analyses and a lack of access to emergency room records.

Recommendation: That Health Canada facilitate the funding of a national study to examine the contribution of domperidone to VA and SCD among women of reproductive age. This research initiative would reflect Health Canada's existing concerns about the growing use of domperidone as a galactogogue and its potential cardiac risks as described in two Safety Reviews.

6.5.2 Improving Health Canada's Policy Responses to Off-label Prescribing

i. Improving Specific Policy Responses to Off-label Prescribing

Health Canada lacks an identifiable and systematic policy and regulatory response to off-label prescribing in the areas of drug approval (Product Monograph content), ADR tracking and signal detection, risk communication messaging and in relation to new Ministerial powers under *Vanessa's Law*. This deficiency exists despite the fact that two Health Canada safety reviews on domperidone have affirmed the cardiac risks of domperidone and the most recent review (211) described the use of domperidone to treat LMS as common and likely to grow in the future.

There are some indications that Health Canada has the flexibility to be able to expand the content of PMs to include common off-label uses, to collect information about off-label uses in ADR reports, to change the wording of risk communication messages so that they can include common off-label uses and to take regulatory actions when safety problems with off-label uses are identified. In order to implement these changes Health Canada would have to allocate more personnel and funding resources to these activities and barriers to the monitoring of ADRS as described in more detail in Section 6.2.5.

Recommendation: That Health Canada undertake the following policy changes to improve the safety and effectiveness of off-label prescribing:

1. Require drug manufacturers to monitor the prevalence of off-label prescribing for the first three years in the case of a new drug being marketed and on an on-going basis for older drugs in order to revise or supplement information on the risks of off-label uses in Product Monographs. This would also include the designation of common off-label uses and risks in the patient information section of the Product Monograph;
2. Identify female gender as an independent risk factor in Product Monographs for all QT-prolonging drugs;
3. Make any safety reports prepared by Health Canada freely accessible on Health Canada's website;
4. Revisit the definition of what constitutes CBI so that information in safety reports is more accessible, including information that is already public, safety research on the product undertaken by Health Canada and other regulators and options for actions arising from the report;
5. Ensure that allied professionals who support breastfeeding mothers, such as lactation consultants through their professional association, the Canadian Lactation Consultants Association, routinely receive risk communication messages related to prescription drugs from Health Canada;
6. Explicitly identify common off-label uses and their risks to relevant populations in safety advisories/warnings issued by Health Canada or the MAH at the direction of Health Canada;
7. Clarify the wording in *Vanessa's Law* to specify that ministerial powers to order safety studies when a safety risk becomes apparent or to take other regulatory measures, applies to both approved and unapproved drug uses. This will require that regulations be changed through cabinet approval.

6.5.3 Improving the Safety, Efficacy and Transparency of Off-label Prescribing

i. Development of Guidelines to Assist Clinicians in Off-label Prescribing Decisions.

Off-label prescribing is legal because it is the provinces that regulate the practice of medicine through professional regulatory bodies, such as the Colleges of Physicians and Surgeons. It is ultimately prescribers who have the authority to determine whether evidence supports the benefits and risks of prescribing an off-label drug.

Findings from my research indicate that domperidone was being prescribed to mothers with LMS without clear evidence of its effectiveness. Doses over Health Canada's safety guidelines for domperidone were commonly prescribed despite the cardiac risks of domperidone being dose-related. These findings suggest that a clearer set of guidelines for assessing the risks and benefits of specific

off-label uses could be helpful for clinicians in their assessment of whether the off-label prescribing of drugs such of domperidone are safe, effective and necessary because no other effective treatment approaches exist. These criteria could also provide a useful set of concepts for members of the public to consider prior to using an off-label drug.

The research literature indicates a growing concern about off-label prescribing leading to recommendations that the use of off-label drugs be assessed with more scrutiny and rely on higher levels of evidence (52, 55,5 6). Aronson and Ferner (52) have specified specific patient, condition and evidence factors to consider prior to making a decision to prescribe an off-label drug.

Recommendation: That professional colleges such as the College of Physicians and Surgeons of British Columbia and the British Columbia College of Nurses and Midwives undertake awareness campaigns with their members to provide more information about off-label prescribing, (for example, the general lack of evidence for many of these uses), and develop and promote explicit guidelines for clinicians to help them assess the value, safety and effectiveness of any off-label uses they might consider. These guidelines would include an assessment of the personal characteristics of the patient such as age, the seriousness/life-threatening nature of the health condition, whether alternative accessible treatments are available, whether there is high quality evidence on the effectiveness and safety of the OLU being considered, whether there is the capacity to collect and assess ADRs from the drug's use and whether patients and clinicians can enter into an informed consent process before an off-label drug is prescribed.

ii. Improving the Transparency of Off-Label Prescribing through Provincial Professional Associations.

Patients are not well informed about the practice of off-label prescribing. Most mothers participating in the survey were not aware of what an off-label or unapproved use means. Research suggests that parents, who are advised that an off-label drug may be prescribed to their children, tend to be more cautious about its use. Other research suggests that off-label use should be discussed with patients before it occurs because of the concerns about the potential risks of off-label uses.

Recommendation: The practice of medicine is regulated by the provinces through provincial professional associations. It is recommended that provincial Colleges of Physicians and Surgeons, Pharmacists and Nurses and Midwives, where these allied professionals have the mandate to prescribe, recommend that prescribers undertake a transparent and informed consent process with their patients or clients before prescribing a drug for an off-label use. This would include a discussion of the unapproved status of the drug for this indication, its potential risks and effectiveness, availability of other treatments, and the current evidence base for the drug.

6.5.4 Improvements to Breastfeeding Support Services and Education in the Community

i. Prioritization of Breastfeeding Support Services at the Community Level

Many of the mothers who were interviewed commented on the need for more breastfeeding information and support prior to and after the birth of their babies. All but one of the mothers gave birth in a hospital and half of them were discharged from hospital within twenty-four hours. This was before their milk supply was established and while they still needed information and support about the lactation process, the correct latching of their infant at the breast and how to interpret infant needs and behavioural cues. About 3% of women in Canada have planned home births (246) and, for most of these births, midwives are tasked with providing postpartum care for up to six weeks.

The move from the hospital to the community led to a disruption in the continuity of care and the fragmentation of services for mothers when they were feeling tired, overwhelmed and vulnerable. Consistent personal support and information about breastfeeding appears to increase a mother's breastfeeding self-efficacy and confidence and is associated with longer-term breastfeeding.

The multiple healthcare providers who were involved in supporting the mother often provided contradictory advice which some mothers found confusing and disempowering. Some of the mothers also reported decreased services available through public health centres in BC and a lack of access to lactation consultants unless they were privately hired for a fee.

Recommendation: That the BC Ministry of Health prioritize the delivery of breastfeeding education and support services to breastfeeding mothers at the community level. Services would include expanded opportunities for breastfeeding education prior to and after the birth and ensuring access to public health nurse teams with the capacity to make home visits after a mother is discharged from the hospital, the facilitation of regular peer- to-peer support groups and access to free lactation counsellors through public health centres, if mothers require them.

ii. Support for Safe and Effective Approaches to Increase Milk Supply

There are many factors related to the medicalization of breastfeeding that appeared to drive the off-label prescribing of domperidone to treat LMS. These factors included the over-diagnosis of LMS by extending the definition of LMS to cover both mild and more serious conditions the medical management of the condition, including early intervention with technologies, the visual measurement f milk volume from pumping (which intimidated some mothers), and the focus on breastmilk as a product rather than focusing on it as natural process reflecting the mother/infant relationship.

Almost all of the mothers found attempts to deal with their milk supply problems in the early postpartum period to be exhausting, stressful and disempowering. The early diagnosis of LMS among most of the mothers, followed by early technological interventions such as the introduction of formula,

extensive pumping schedules and domperidone affected mothers' ability to achieve their early breastfeeding goals.

Recommendation: It is recommended that the following educational and clinical practices be adopted in order to support non-pharmacological approaches to breastfeeding:

1. That health professionals who provide support to those who are breastfeeding be made aware of the limited efficacy of domperidone for treating LMS, the specific lack of evidence for the efficacy of doses over 30 mg/day and the cardiac risks of the drug. It is suggested that this information be provided through professional regulatory bodies and that every opportunity to repeat this message in formal communications, guidelines, educational sessions and through other communication methods be used;
2. That the College of Physicians and Surgeons of British Columbia and the BC College of Nurses and Midwives recommend that women who are prescribed domperidone to treat LMS be required to undergo an ECG prior to it being used;
3. That there be the adoption of evidence-based standards by appropriate professional bodies such as the College of Physicians and Surgeons of BC and the BC College of Nurses and Midwives as well as organizations such as the BC and Canadian Lactation Consultant Associations (BCLCA, CLCA), and the BC Baby Friendly Network, that support breastfeeding, to clarify best practices for the diagnosis of LMS with an understanding of the variability in postpartum weight gain among infants.

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APPENDIX I: CLINICIANS' ONLINE SURVEY QUESTIONS

USING DOMPERIDONE TO TREAT INSUFFICIENT BREAST MILK SUPPLY

ONLINE PHYSICIANS'* AND MIDWIVES' SURVEY QUESTIONS

The health benefits of breastfeeding have long been recognized and most new mothers plan to breastfeed. However, many stop breastfeeding early because of concerns about having enough breast milk. I am asking family physicians and midwives to complete this 5-minute survey in order to learn more about how insufficient milk supply among mothers with full-term babies is diagnosed and treated in BC. A focus of this survey is on the use of domperidone and other methods to increase milk supply. This is the first survey in Canada to examine clinician experiences with insufficient milk supply, domperidone and other methods that are being used to treat it.

Your participation in this survey is voluntary and you are free to skip any survey questions or leave the survey at any time. Your answers are confidential. They will not be reported individually and cannot be attributed to you personally.

If you have any questions or comments about the survey please contact me.

Thank you for participating in this important research.

Janet C. Currie MSW

PhD candidate, Interdisciplinary Studies Graduate Program/School of Nursing/UBC

Research Co-investigator and Coordinator

BACKGROUND QUESTION: All survey respondents

1. In the past year, approximately how many patients or clients with full-term babies have you treated for low milk supply?

a. ❒ Over 20
b. ❒ 11-20
c. ❒ 6-10
d. ❒ 1-5
e. ❒ None

2. When a patient or client appears to be experiencing low milk supply, how frequently do you use the following approaches or information to assess whether this is the case?

	APPROACHES	Always Use	Most of the Time	About Half the Time	Once in a While	Never
a.	Test/retest weighing of baby after feedings	O	O	O	O	O
b.	Baby cues reported by patient or client (e.g. fussiness, failure to latch)	O	O	O	O	O
c.	Measurement of breast milk volume (pumping and measurement)	O	O	O	O	O
d.	Patient/client reports of lack of milk /empty breasts	O	O	O	O	O
e.	Count of number of wet diapers per day	O	O	O	O	O
f.	Tracking of weight on a growth curve	O	O	O	O	O
g.	Other: Please include: _____	O	O	O	O	O

3. Which of the following approaches do you recommend or prescribe for clients or patients with low milk supply? <u>Please check all the approaches you use, no matter how frequently.</u>

a. ❒ Increase frequency of breastfeeding or pumping
b. ❒ Reduce supplementation
c. ❒ Provide information on improved breastfeeding techniques (e.g. proper latch)
d. ❒ Provide reassurance/information about lactation
e. ❒ Discuss the impact of birth and personal experiences on breastfeeding
f. ❒ Recommend non-prescription galactogogues (e.g. herbal teas or remedies)
g. ❒ Refer patient to a lactation consultant/ other breastfeeding expert
h. ❒ Prescribe/recommend domperidone ➔ If question checked respondents will be directed to question 4, if not checked respondents will be directed to question 9

4. **Do you sometimes recommend or prescribe domperidone to patients or clients with low milk supply?**

    a. ❒ Yes
    b. ❒ No

Questions for clinicians who recommend or prescribe domperidone

5. **In the past two years, what percentage of your patients or clients who have had low milk supply have you treated or recommended treatment with domperidone?**

    a. ❒ Most (over 75%)
    b. ❒ Many (50-74%)
    c. ❒ Some (25-49%)
    d. ❒ A few (under 25%)

6. **What sources of information are <u>most useful</u> in terms of providing information about the efficacy and safety of domperidone to treat low milk supply? Please check all resources that you have found to be useful. Please add other resources you find useful to the end of this list and check this box.**

    a. ❒ Cochrane or other independent systematic reviews
    b. ❒ Other research published in the medical literature
    c. ❒ CPS (Compendium of Pharmaceutical Specialties)
    d. ❒ Consensus statements/guidelines by breastfeeding experts
    e. ❒ Patient feedback
    f. ❒ Textbooks on breastfeeding (e.g. Breastfeeding: A Guide for the Medical Profession)
    g. ❒ Advice from colleagues
    h. ❒ Workshops/seminars/lectures
    i. ❒ Information from professional associations or colleges
    j. ❒ Online sources/internet/website (e.g. Up-to-Date)
    k. ❒ Personal clinical experience with the drug
    l. ❒ Health Canada safety reviews/advisories
    m. ❒ Information from drug manufacturers
    n. ❒ Other (please list) _____
    o. ❒ Other (please list) _____

7. How frequently do you undertake or recommend the following types of patient/client assessments when considering the use of domperidone to treat low milk supply.

Type of Assessment	Always	Most of the time	About half of the time	Once in a while	Never
a. Patient/client's previous cardiac history (e.g. arrhythmias)	○	○	○	○	○
b. Current use of QT-prolonging drugs	○	○	○	○	○
c. ECG	○	○	○	○	○

8. What daily dose level of domperidone do you consider to be most effective in successfully treating insufficient milk supply?

a. ❒ 30 milligrams/day
b. ❒ 60 milligrams/day
c. ❒ 80 milligrams/day
d. ❒ More than 80 milligrams/day
e. ❒ Other (please enter) _____

9. Approximately what percentage of your patients/clients are able to breastfeed without supplementation with formula or donor milk after being treated with domperidone?

a. ❒ Almost all (over 75%)
b. ❒ Many (50-74%)
c. ❒ Some (25-49%)
d. ❒ A few (under 25%)
e. ❒ None
f. ❒ Unable to estimate

Questions for all clinicians

10. Within the past two years, what percentage of patients/clients with concerns about insufficient milk supply have initiated discussions with you about using domperidone prior to your mentioning it?

a. ❒ Over half
b. ❒ Between 25-50%
c. ❒ Less than 25%
d. ❒ Never happens

11. The use of domperidone to treat low milk supply is:

a. ❒ An on-label use b. ❒ An off-label use ❒ Don't know/uncertain

12. Health Canada issued Safety Advisories on the cardiac risks of domperidone in 2012 and 2015. Are you familiar with one or both of these advisories?

a. ❒ Yes (Respondents will be directed to Question 12)

b. ❒ No (Respondents will be directed to Question 13)

13. How applicable do you consider Health Canada's Safety Advisories on domperidone to be when domperidone is being used to treat low milk supply?

a. ❒ Fully applicable

b. ❒ Quite applicable

c. ❒ Somewhat applicable

d. ❒ Not applicable

14. Do you feel that domperidone poses any health risks to patients/clients when they are taking it to increase breastmilk supply?

a. ❒ No significant risks

b. ❒ Minimal risks

c. ❒ Moderate risks

d. ❒ Significant risks

e. ❒ Uncertain

15. Do you feel that domperidone passing through breast milk poses any health risks to babies?

a. ❒ No significant risks

b. ❒ Minimal risks

c. ❒ Moderate risks

d. ❒ Significant risks

e. ❒ Uncertain

16. Do you have any other comments or recommendations related to the use of domperidone to address insufficient milk supply?

_____
_____
_____

CLINICIAN DATA – ALL RESPONDENTS

17. How many years have you been in practice?
    a. ❒ Less than 10
    b. ❒ 10-19
    c. ❒ 20-29
    d. ❒ 30+

18. What is your profession?
    a. ❒ Family Physician b. ❒ Midwife c. ❒ Other _____

19. What is your gender?
    a. ❒ Male ❒ Female ❒ Transgender ❒ Other ❒ Prefer not to say

20. If you are a midwife, what is the main geographical area that you practice in? If you are a physician, what is the name of your Division of Family Practice?

    _____

***Additional question added to the Physician's Survey – for all physicians- not asked in Midwives' Survey: In general, how comfortable are you at assessing and treating breastfeeding problems like low milk supply?**

- ❒ Very comfortable
- ❒ Somewhat comfortable
- ❒ Not very comfortable
- ❒ Not comfortable at all

Thank you! You have come to the end of the survey. After you press submit you will be directed to another survey page that provides you with the opportunity to enter into a draw to win an amazon.ca gift card worth $100.00. Your entry into the draw is confidential and is not linked with your survey answers.

November 30, 2017

APPENDIX II: MOTHERS' INTERVIEW GUIDE

BREASTFEEDING PARTICIPANTS INTERVIEW GUIDE

USING DOMPERIDONE TO TREAT INSUFFICIENT BREAST MILK SUPPLY

Thank you again for your willingness to be interviewed for my PhD research. The purpose of this interview is to discuss your experiences with breastfeeding and with domperidone. Domperidone is prescribed frequently in BC to address insufficient breast milk supply, however, this is the first research in BC that has asked those who breastfeed about their experiences with insufficient milk supply and their use of domperidone and other methods to address it. I hope that the findings from this research will be useful to those who breastfeed, their families and healthcare providers. I am also conducting a survey of midwives and family physicians on how they address insufficient breast milk supply, including their use of domperidone.

The consent form you have signed explained how your rights and confidentiality as a research participant are being protected. Today I will be recording this interview. I want to assure you again that your participation in this survey is confidential and that any of the comments you provide today will never be attributed to you.

If you have any concerns about the interview, if you want to take a break or stop the interview at any time, please let me know. You do not have to answer any questions that make you feel uncomfortable. Do you have any questions before we begin?

SEMI-STRUCTURED INTERVIEW GUIDE

1. Introductions – general conversation to set the tone for the interview (e.g. Asking about the community respondent lives in, how old the baby is and whether the participant has any other children)

2. Could you tell me a little about your baby (name) and (his/her) birth?
   a. When and where was your baby born?
   b. Could you tell me a bit about your baby's birth and the time after s/he was born?
   c. How did you feel during and after the birth?

3. Could you describe your initial experiences with breastfeeding?
    a. When did you first try breastfeeding?
    b. When did your milk come in?

4. Did you receive any kind of support or information to help you breastfeed either before or after your baby was born? What was the impact of this support and/or information?
    a. What kind of information or support did you receive?
    b. Where or from whom did you receive this information?
    c. Did the presence or lack of support and information you received have any impact on your breastfeeding experience or decision to use domperidone?

5. Can you talk a little about when any concerns about your breast milk supply arose, who identified this and the approaches you used to address it?
    a. What were your concerns about your breast milk supply and when did these arise?
    b. Who helped you identify them?
    c. Were any specific tests done to assess your breast milk supply?

6. Could you describe how you first heard about domperidone, why you decided to use it and what information you learned about the drug?

7. How frequently did you use domperidone and what was your pattern of use?
    a. How long did you use domperidone?
    b. Are you still using domperidone?
    c. Were there times when you used it more or less frequently?
    d. Can you remember what your usual daily dose level of domperidone was? Was the dose changed at any time?

8. Before you were first prescribed domperidone, did a healthcare provider discuss your medical history with you or recommend any tests?
    a. What aspects of your history were discussed?
    b. What tests were recommended?

9. Can you tell me whether there were any effects of using domperidone on you and your baby?
    a. Can you talk a little about whether domperidone affected your experience of breastfeeding?
    b. Did taking domperidone have any effect on your supply of breast milk?
    c. Did you experience any other impacts of using domperidone, for example, on your use of formula?
    d. Do you or your baby experience any symptoms or side effects from using domperidone or from discontinuing it?

10. All drugs that are prescribed in Canada are tested and approved to treat specific health conditions. However once a drug is available in Canada, it can also be prescribed for other conditions if a doctor or midwife believes it could be helpful. This is called off-label prescribing. About 20% of all drugs are prescribed off-label. Domperidone has been tested and approved in Canada only for stomach and intestinal problems but it is commonly prescribed in BC to increase breast milk supply.

    8. Were you aware that using domperidone to address insufficient milk supply is an off-label use?

    9. I would be interested in your opinions about the off-label prescribing of domperidone when it is used to treat breast milk insufficiency.

    10. Can you comment on any factors either in society, within your family or in your personal life that that you feel may have affected your breastfeeding experience or your decision to use domperidone? These factors could include societal expectations about breastfeeding, pressures from family or friends or issues like work stress.

14. Additional Questions

I would like to ask a few final specific questions about you that may have not come up in the interview. Your answers will provide some background to my research but will not identify you.

a. Using the following age groupings, can you tell me what age you were when you had the baby we were discussing today?

- ❒ Under 25
- ❒ From 25 to 30
- ❒ From 31- 36
- ❒ Over 37

b. What region in BC do you live in?

- ❒ Vancouver
- ❒ Fraser Valley
- ❒ Vancouver Island
- ❒ Interior of BC

This completes the questions I had for you today. Do you have final comments or observations about your experiences with breastfeeding or domperidone?

Thank you so much for participating in this interview today. Your experiences and observations will be valuable to others who breastfeed, their families and healthcare providers.

In case I need to clarify some of the points you made, would it be alright if I contact you by email?

Thank you again.

September 30, 2017