Frequency and Impact of Drug-Drug Interactions Among Non-Elderly Community-Dwelling Adults in Quebec, Canada

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DEDICATION

I dedicate this thesis to the memory of my supervisor and mentor, Dr. Pierre Pluye.

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LIST OF ABBREVIATIONS

ADR	Adverse drug reactions
AHFS	American Hospital formulary service
AUC	Area under the receiver operator curve
AZCERT	Arizona Centre for Education and Research on Therapeutics
BDCU	Banque de données communes des urgences (Quebec emergency department database)
BIOSIS	Biosciences Information Service
CAN-AIM	Canadian Network for Advanced Interdisciplinary Methods for Comparative Effectiveness Research
CDS	Clinical decision support systems
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CNODES	Canadian Network for Observational Drug Effect Studies
COCI	Bice-Boxerman continuity of care index
CSBE	Commissaire à la santé et au bien-être du Québec (Health and Welfare Commissioner of Quebec)
CYP	Cytochrome P450 family of enzymes
DDD	Defined daily doses
DDI	Drug-drug interaction
DIN	Drug identification number
DSEN	Drug Safety and Effectiveness Network
ECG	Electrocardiogram
EQUATOR	Enhancing the Quality and Transparency Of Health Research
ER	Emergency room
FDA	Food and Drug Administration (U.S.)
FP	Family physician
GLMM	Generalized linear mixed modeling
GMF	Groupe de médecine de famille

hERG	Human ether a go-go gene
INESS	Institut national d'excellence en santé et en services sociaux (Quebec national institute for excellence in health and social services)
INSPQ	Institut national de santé publique du Québec (Quebec national public health institute)
ISMP	Institute for safe medication practices
LASSO	Least absolute shrinkage and selection operator
MED-ÉCHO	Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (Quebec hospital discharge database)
MSSS	Ministère de la Santé et des Services sociaux (Quebec Ministry of Health and Social Services)
NOC	Notice of compliance
NOC/c	Notice of compliance with conditions
ONC	U.S. Office of the National Coordinator for Health Information Technology
OTC	Over-the-counter drugs
PBPK	Physiologically based pharmacokinetic models and simulations
PI	Prediction interval
PPI	Proton pump inhibitors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAMQ	Régie de l'assurance maladie du Québec (Quebec Health Insurance management agency)
RERI	Relative excess risk due to interaction
ROC	Receiver operator curve
SEARCH	Active Surveillance and Evaluation of Adverse Reactions in Canadian Healthcare
SFINX	Swedish-Finnish interaction X-referencing knowledge base
UPC	Usual provider of care index

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ABSTRACT

Background: Adverse events due to medications are estimated to be among the top causes of death in high-income nations. While some adverse drug effects are idiosyncratic in nature and thus unpreventable, drug-drug interactions (DDI) are a known and preventable source of adverse drug effects. The risk of harm from exposure to drug-drug interactions has been vastly documented for specific patient groups, such as the elderly, whereas relatively scant work has been conducted on the frequency of exposure to drug-drug interactions and their impact in the health and well-being of non-elderly adult community-dwelling patients in Canada.

Overall aim and specific objectives: The overall aim of this work was to advance the knowledge on the frequency and impact of exposure to drug-drug interactions among community-dwelling non-elderly adults using publicly owned administrative health data earmarked for enhancing the quality of health services offered in the province of Quebec. The specific objectives were to (1) produce a knowledge synthesis on the prevalence and rate of exposure to drug-drug interactions among community-dwelling non-elderly adults around the world; (2) estimate the prevalence to high-priority drug-drug interactions among community-dwelling, non-elderly adult outpatients in the Canadian province of Quebec; (3) identify demographic and health system variables associated with the subsequent risk of exposure to high-priority drug-drug interactions; (4) assess whether exposure to high-priority drug-drug interactions increases the risk of experiencing an adverse health outcome.

Methods: *Objective 1*. A systematic literature review was conducted following the recommendations presented in the Cochrane Handbook for Systematic Reviews of Interventions and the Joanna Briggs' Institute guidance for systematic reviews of observational epidemiological studies reporting prevalence data. The manuscript is presented using the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All empirical studies measuring the frequency of exposure to drug-drug interactions among non-elderly outpatients and presenting age-stratified frequency of drug-drug interactions were included. Studies were appraised using a specialized checklist on risks of bias of observational studies. Meta-analyses were conducted to pool prevalence proportions and rates of exposure to drug-drug interactions. Subgroup analyses by predefined study characteristic were conducted. *Objectives 2 and 3.* An anonymized cohort composed of a random sample of 5% of the database population of community-dwelling adults in Quebec with continuous coverage by the public drug insurance of Quebec's public health insurer (RAMQ) between April 1, 2014, and March 31, 2017, was constructed. Demographic and health service use data were extracted for this cohort and used to construct the measures of multimorbidity, continuity of care, and index of social and material deprivation. All prescription medications obtained from pharmacy claims were converted to active ingredients (hereafter, drugs), and individuals were assumed to be exposed to each drug starting on the date of the claim and for the duration specified in the claim. A list of high-priority drug pairs predicted to interact with each other was created from the list of high priority drug-drug interactions commissioned by the Office of the National Coordinator for Health Information Technology in the United States. This list was used to identify exposure to drug-drug interactions among overlapping drug exposures for each individual in the cohort. The Superlearner algorithm was used to assess whether health system use variables predicted future exposure to high-priority drug-drug interactions, and a measure of variable importance was used to rank the variables by their importance in predicting the risk of exposure to a drug-drug interaction. *Objective 4.* A dynamic cohort was constructed using the same cohort as in objectives 2 and 3. Individuals exposed to one of eleven drugs of interest were followed from the first day of exposure to a drug of interest for up

to 24 months or until a visit to the emergency department, a hospitalization, or death. Cox proportional hazards with time-varying drug exposures were conducted to assess the association between exposure to one of four drug-drug interactions (proton pump inhibitors + citalopram, proton pump inhibitors + domperidone, proton pump inhibitors + quetiapine, and proton pump inhibitors + ciprofloxacin).

Results: *Objective 1.* In the systematic literature review, a total of 5,449 records were identified, of which 28 studies measuring exposure to drug-drug interactions among community-dwelling non-elderly adults were included in a descriptive synthesis. Twelve studies reporting the proportion of non-elderly adult outpatients exposed to drug-drug interactions among those exposed to two or more drugs and were included in the meta-analysis. The pooled prevalence of exposure to DDI among those exposed to two or more drugs was 0.18 (95% CI 0.09 – 0.35; PI 0.01 – 0.80); the pooled rate of exposure to at least one drug-drug interaction of these same studies was 20.12 DDI per 1,000 person-months exposed to two or more drugs (95% CI 7.25 to 55.84 DDI per 1,000 person-months, PI 0.57 – 152.07). These prediction intervals suggest that 95% of similar future studies will find a prevalence of exposure to drug-drug interactions between 1 and 80% and indicate the need for more research on this area. *Objective 2.* Based on the cohort constructed from the RAMQ prescription claims database, more than half (54.1%) of the 63,834 community-dwelling adults in the cohort were exposed to two or more drugs during the 12-month study period, and 7,498 (11.75% of the study population) were exposed to at least one drug-drug interaction for at least one day, with 30,385 episodes of exposure to drug-drug interactions (median duration of 15 days, IQR 50, range 1 to 365 days). A total of 850 drug-drug interaction combinations were found, with the majority involving two drugs with known or conditional risk of leading to long QT syndrome (accounting for 760/850 [89.4%] of drug-drug interactions). *Objective 3*. The machine

learning approach led us to predict prevalent drug-drug interaction exposures over 12 months with an AUC of 0.90, and incident (new) exposures to drug-drug interactions with an AUC of 0.78 on test data, showing that exposure to drug-drug interactions can be predicted from their use of the healthcare system. *Objective 4.* Three of the four drug-drug interactions investigated (proton pump inhibitors in combination with citalopram/escitalopram, domperidone, and ciprofloxacin) led to a greater increase in daily hazard for an adverse event than would be expected from the combination of the two drugs if there was no interaction. The marginal hazard ratios (95% CI) for each added defined daily dose of victim drug in the presence of one defined daily dose of proton pump inhibitor were 1.66 (1.36 – 2.01), 1.76 (1.21 -2.56) and 1.40 (1.03 – 1.77) for citalopram, domperidone, and ciprofloxacin, respectively. Exposure to proton pump inhibitors and quetiapine was not associated with an increased hazard for an adverse event (current use HR 1.09, 95% CI: 0.66 – 1.78).

Conclusion: this work provides evidence that exposure to DDI varies widely across settings. In Quebec, 1 in 8.5 adults with public drug insurance coverage was exposed to at least one high-priority drug-drug interaction over one year. Encouraging moderation when prescribing, and increased continuity of prescriber and pharmaceutical care may help prevent exposure to drug-drug interactions in this population. Administrative health databases represent a rich source of prescription drug use data that can allow regulators to monitor patient harm following exposure to drug-drug interactions.

RÉSUMÉ

Contexte : Les évènements indésirables liés aux médicaments sont parmi les principaux causes de décès dans les pays à revenu élevé. Bien que certains effets indésirables des médicaments soient de nature idiosyncratique et donc inévitables, les interactions médicamenteuses (IM) sont une source connue et évitable d'effets indésirables des médicaments. Le risque de préjudice lié à l'exposition aux interactions médicamenteuses a été largement documenté pour des groupes de patients spécifiques, tels que les personnes âgées, alors que relativement peu de travaux ont été menés sur la fréquence de l'exposition aux interactions médicamenteuses et leur impact sur la santé et le bien-être des patients adultes non âgés vivant dans la communauté au Canada.

But général et objectifs spécifiques : Le but général de ce travail était de faire progresser les connaissances sur la fréquence et l'impact de l'exposition aux interactions médicamenteuses chez les adultes non âgés vivant dans la communauté à l'aide de données administratives de santé publiques dans la province de Québec. Les objectifs spécifiques étaient de (1) produire une synthèse des connaissances sur la prévalence et le taux d'exposition aux interactions médicamenteuses chez les adultes non âgés vivant dans la communauté à travers le monde ; (2) estimer la prévalence des interactions médicamenteuses prioritaires chez les patients adultes non âgés vivant dans la communauté dans la province canadienne du Québec ; (3) identifier les variables démographiques et du système de santé associées au risque ultérieur d'exposition à des interactions médicamenteuses prioritaires ; (4) évaluer si l'exposition à des interactions médicamenteuses prioritaires augmente le risque de subir un effet indésirable sur la santé.

Méthodes : *Objectif 1*. Une revue systématique de la littérature a été menée conformément aux recommandations présentées dans le *Cochrane Handbook for Systematic Reviews of Interventions* et dans les directives de l’institut Joanna Briggs pour les revues systématiques d'études

épidémiologiques observationnelles rapportant des données de prévalence. Le manuscrit est présenté en utilisant les lignes directrices PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Toutes les études empiriques mesurant la fréquence d'exposition aux interactions médicamenteuses chez les patients ambulatoires non âgés et présentant la fréquence stratifiée selon l'âge des interactions médicamenteuses ont été incluses. Les études ont été évaluées à l'aide d'une liste de contrôle spécialisée sur les risques de biais des études observationnelles. Des méta-analyses ont été menées pour regrouper les proportions de prévalence et les taux d'exposition aux interactions médicamenteuses. Des analyses de sous-groupes par caractéristique d'étude prédéfinie ont été réalisées. *Objectifs 2 et 3.* Une cohorte anonymisée composée d'un échantillon aléatoire de 5 % de la population de la base de données des adultes vivant dans la communauté au Québec et couverts en continu par le régime publique d'assurance médicament de la Régie de l'assurance maladie du Québec (RAMQ) entre le 1er avril 2014, et 31 mars 2017, a été construit. Les données démographiques et d'utilisation des services de santé ont été extraites pour cette cohorte et utilisées pour construire les mesures de la multimorbidité, la continuité des soins et l'indice de défavorisation sociale et matérielle. Tous les médicaments sur ordonnance obtenus à partir des réclamations pharmaceutiques ont été convertis en ingrédients actifs (ci-après, les médicaments), et les personnes ont été supposées être exposées à chaque médicament à partir de la date de la réclamation et pendant la durée spécifiée dans la réclamation. Une liste d'interactions médicamenteuses prioritaires a été créée à partir de la liste des interactions médicamenteuses hautement prioritaires commandée par le Bureau du coordinateur national des technologies de l'information sur la santé aux États-Unis. Cette liste a été utilisée pour identifier l'exposition aux interactions médicamenteuses parmi les expositions aux médicaments qui se chevauchent pour chaque individu de la cohorte. L'algorithme Superlearner a été utilisé pour

évaluer si les variables d'utilisation du système de santé prédisaient l'exposition future à des interactions médicamenteuses hautement prioritaires, et une mesure de l'importance de chaque variable a été utilisée pour classer les variables selon leur importance dans la prédiction du risque d'exposition à une interaction médicamenteuse. *Objectif 4.* Une cohorte dynamique a été construite en utilisant la même cohorte que dans les objectifs 2 et 3. Les personnes exposées à l'un des onze médicaments d'intérêt ont été suivies depuis le premier jour d'exposition à un médicament d'intérêt jusqu'à 24 mois ou jusqu'à une visite aux urgences, une hospitalisation ou un décès. Une analyse utilisant une régression à risque proportionnel de Cox avec des expositions médicamenteuses variables dans le temps a été menée pour évaluer l'association entre l'exposition à l'une des quatre interactions médicamenteuses (inhibiteurs de la pompe à protons + citalopram, inhibiteurs de la pompe à protons + dompéridone, inhibiteurs de la pompe à protons + quétiapine et inhibiteurs de la pompe à protons + ciprofloxacine).

Résultats : *Objectif 1.* Dans la revue systématique de la littérature, 5 449 dossiers ont été identifiés, dont 28 études mesurant l'exposition aux interactions médicamenteuses chez les adultes non âgés vivant dans la communauté ont été incluses dans une synthèse descriptive. Douze études rapportant la proportion de patients externes adultes non âgés exposés aux interactions médicamenteuses parmi ceux exposés à deux médicaments ou plus ont été incluses dans la méta-analyse. La prévalence combinée de l'exposition aux interactions médicamenteuses parmi les personnes exposées à deux drogues ou plus était de 0,18 (IC à 95 % 0,09 - 0,35 ; IP 0,01 - 0,80) ; le taux combiné d'exposition à au moins une interaction médicamenteuse de ces mêmes études était de 20,12 IM pour 1 000 personnes-mois exposées à deux médicaments ou plus (IC à 95 % 7,25 à 55,84 IM pour 1 000 personnes-mois, IP 0,57 – 152,07). Ces intervalles de prédiction suggèrent que 95 % des études futures similaires trouveront une prévalence d'exposition aux interactions

médicamenteuses d’entre 1 % et 80 % et indiquent la nécessité de poursuivre les recherches dans ce domaine. *Objectif 2*. D'après la cohorte construite à partir de la base de données des réclamations d'ordonnances de la RAMQ, plus de la moitié (54,1 %) des 63 834 adultes vivant dans la communauté de la cohorte ont été exposés à deux médicaments ou plus au cours de la période d'étude de 12 mois, et 7 498 (11,7 % de la population étudiée) ont été exposés à au moins une interaction médicamenteuse pendant au moins un jour, avec 30 385 épisodes d'exposition à des interactions médicamenteuses (durée médiane de 15 jours, IQR 50, intervalle de 1 à 365 jours). Au total, 850 combinaisons d'interactions médicamenteuses ont été trouvées, la majorité impliquant deux médicaments présentant un risque connu ou conditionnel d'entraîner un syndrome du QT long (représentant 760/850 [89,4 %] des interactions médicamenteuses). *Objectif 3*. L’approche d'apprentissage automatique nous a conduit à prédire les expositions prévalentes aux interactions médicamenteuses sur 12 mois avec une AUC de 0,90, et les expositions incidentes (nouvelles) aux interactions médicamenteuses avec une AUC de 0,78 sur les données de test, montrant que l'exposition aux interactions médicamenteuses peut être prédite à partir de l’utilisation du système de santé. *Objectif 4.* Trois des quatre interactions médicamenteuses étudiées (inhibiteurs de la pompe à protons en association avec citalopram/escitalopram, dompéridone et ciprofloxacine) ont entraîné une augmentation du risque quotidien d'événement indésirable plus importante qu’attendu de la combinaison des deux médicaments s'il n'y avait pas d'interaction. Les rapports de risque marginaux (IC à 95 %) pour chaque dose quotidienne définie ajoutée de médicament victime en présence d'une dose quotidienne définie de pompe à protons étaient de 1,66 (1,36 – 2,01), 1,76 (1,21 -2,56) et 1,40 (1,03 – 1,77) pour le citalopram, la dompéridone et la ciprofloxacine, respectivement. L'exposition aux inhibiteurs de la pompe à

protons en combinaison avec la quétiapine n'a pas été associée à un risque accru d'événement indésirable (utilisation actuelle HR 1,09, IC à 95 % : 0,66 – 1,78).

Conclusion : ce travail fournit des preuves que l'exposition aux interactions médicamenteuses varie considérablement d'un contexte à l'autre. Au Québec, 1 sur 8,5 des adultes non âgés vivant dans la communauté et bénéficiant d'une couverture par le régime général d'assurance médicament a été exposé à au moins une interaction médicamenteuse prioritaire sur une année. Encourager la modération lors de la prescription et une continuité accrue des soins du prescripteur et des services pharmaceutiques pourraient aider à prévenir l'exposition aux interactions médicamenteuses dans cette population. Les bases de données administratives sur la santé représentent une riche source de données sur l'utilisation des médicaments sur ordonnance qui peuvent permettre aux organismes de réglementation de surveiller les préjudices subis par les patients après une exposition à la DDI.

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PREFACE

Details regarding the manuscript-based PhD thesis

This thesis comprises three manuscripts of which I am the first author.

The following paragraphs are quoted from the Faculty of Graduate Studies and Research at McGill University's Guidelines for *Preparation of a Thesis*.

"As an alternative to the traditional format, a thesis may be presented as a collection of scholarly papers of which the student is the first author or co-first author. A manuscript-based doctoral thesis must include the text of a minimum of two manuscripts published, submitted or to be submitted for publication. A manuscript-based Master's thesis must include the text of one or more manuscripts. Articles must be formatted according to the requirements described below. Note that a manuscript-based thesis must follow the general structure of a thesis as explained here. An FAQ explaining the difference between a standard and a manuscript-based thesis is available here.

Manuscripts for publication in journals are frequently very concise documents. A thesis, however, is expected to consist of more detailed, scholarly work. A manuscript-based thesis will be evaluated by the examiners as a unified, logically coherent document in the same way a traditional thesis is evaluated. Publication of manuscripts, or acceptance for publication by a peer-reviewed journal, does not guarantee that the thesis will be found acceptable for the degree sought.

A manuscript-based thesis must:

- be presented with uniform font size, line spacing, and margin sizes (see Thesis Format under Preparation of a Thesis);
- conform to all other requirements listed under Thesis Components on the Preparation of a Thesis page;

- contain additional text that connects the manuscript(s) in a logical progression from one chapter to the next, producing a cohesive, unitary focus, and documenting a single program of research - the manuscript(s) alone do not constitute the thesis;
- stand as an integrated whole.

Any manuscripts that are under review, accepted or published in a journal must be included in your manuscript-based thesis without changes (i.e. identical to the published or submitted versions). The only change is with respect to the font/size which should be the same as the one used for the rest of the thesis for consistency and homogeneity reasons. So each chapter represents a full manuscript and has its own reference list. Then at the end of the thesis, you have a master reference list which includes all the other references cited throughout the other sections of the thesis, mostly within the general introduction but also from the general discussion.

Depending on the feedback of your examiners and/or the oral defence committee, you may be required to make revisions to your thesis before final submission. The committee's comments must be addressed in the connecting text between chapters and/or the discussion section. You must not make any changes to the manuscripts themselves in your final thesis.

In the case of multiple-authored articles, the student must be the first author. Multiple-authored articles cannot be used in more than one thesis. In the case of students who have worked collaboratively on projects, it may be preferable for both students to write a traditional format thesis, identifying individual contributions. Consult this page for information on intellectual property and required permissions/waivers.

In the case of co-first authored articles, only one student can use the article in a manuscript-based thesis and must have a written agreement from the other co-first author student(s)."

Contribution to original knowledge

This is a manuscript-based dissertation which includes three manuscripts. The work presented in this dissertation constitutes original contributions in the field of pharmacoepidemiology and drug safety.

Manuscript 1 (Chapter 4) presents a systematic review and meta-analysis of the prevalence and incidence of exposure to predicted drug-drug interactions among community-dwelling non-elderly adults (19-64 years old) using rigorous methodology.[1, 2] To our knowledge, this is the first systematic review and meta-analysis on this important topic.

Manuscript 2 (Chapter 5) presents the first population-based assessment of exposure to drug-drug interactions among community-dwelling non-elderly adults in Quebec and Canada, addressing an important gap in knowledge. The work presented in this manuscript includes the creation of an evidence based open access database of drug-drug interactions to guide in their identification. This contributes important knowledge regarding the state of exposure to high-priority drug-drug interactions among non-elderly adults in Quebec and the demographic, continuity of care, and health service use variables predicting increased risk of exposure to drug-drug interactions among this population. Having conducted this work as an embedded doctoral fellow in Quebec's National Institute for excellence in health and social services, INESSS, I was able to create the analytical tools needed to allow INESSS to reproduce these analyses.

Manuscript 3 (Chapter 6) presents the first building block for the use of Quebec administrative health data to assess the impact of exposure to high-priority drug-drug interactions in the province. The analytical framework implemented the use of drug exposure duration and daily

dose (obtained from pharmaceutical claims databases) to measure the association between daily exposure to drug-drug interactions and an adverse event in a dose-dependent manner.

Contribution of Authors

As a doctoral candidate and first author on all the manuscripts and chapters included in this dissertation, I was responsible for the conception of the objectives and research protocol, the data preparation, data analysis, interpretation of findings, and presentation of results. I conducted a comprehensive literature review that was used to inform the project development and created the programs for the data preparation and statistical analysis necessary for completing this work using administrative health databases, with the exception of the Index of comorbidity for which I used a macro developed by Quebec's National public health institute (INSPQ). The overall scope of this research was defined in collaboration with Dr. Pierre Pluye and Dr. Christian Rochefort; the relevance and clinical usefulness of the objectives was refined with the feedback of the thesis supervisory committee, including Dr. Edeltraut Kroger, Dr. Caroline Sirois, and Dr. Elham Rahme. The statistical analyses were developed in collaboration with Dr. Michal Abrahamowicz and Dr. Tibor Schuster. Dr. Mike Benigeri from INESSS helped in the data extraction and interpretation. Dr. Denis Roy helped contextualize the project goals. Drs. Benigeri and Roy were instrumental for the establishment of the project of drug-drug interactions among adults in Quebec as part of the triennial activity plan of INESSS (2019-2022).

I am grateful for the comments and supervision provided by Dr. Pierre Pluye, Dr. Tibor Schuster, and members of my thesis committee. I describe the specific author contributions to each of the chapters of this thesis below.

Chapter 1. Introduction

This chapter presents the project and its contributions. Dr. Pierre Pluye provided helpful comments and suggestions for this chapter.

Chapter 2. Background and literature review

I am the first author of this chapter presenting a comprehensive literature review. Dr. Pierre Pluye provided helpful comments and suggestions for this chapter.

Chapter 3. Methods

I am the first author of this chapter. Christian Rochefort and Michal Abrahamowicz provided helpful suggestions to the methods during the protocol stage. Dr. Pierre Pluye and Dr. Tibor Schuster provided helpful comments and suggestions for this chapter.

Chapter 4. Frequency of exposure to potential drug-drug interactions among community-dwelling, non-elderly adults: A systematic literature review and meta-analysis of observational studies (manuscript # 1)

I am the first author of this chapter. Dr. Hong acted as the second reviewer in the study selection and data extraction while Drs Sirois, Kroger, Rochefort, and Pluye reviewed the text and provided helpful comments.

Chapter 5. Exposure to High-Priority Drug-Drug Interactions among non-elderly community dwelling adults in Quebec (manuscript # 2)

I am the first author of this chapter. Dr. Tibor Schuster and Dr. Delphine Bosson-Rieutort helped in the analysis and result interpretation and image generation. Dr. Pierre Pluye, Dr. Tibor Schuster, Dr. Kroger, and Dr. Bosson-Rieutort provided helpful comments to the text. Dr. Benigeri and Dr.

Roy facilitated the data access, helped with the operationalisation of variables, and helped to contextualize the findings.

Chapter 6. Impact of exposure to high-priority drug-drug interactions among non-elderly community-dwelling non-elderly adults (manuscript # 3)

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Chapter 7. Discussion

I am the first author of this chapter. Dr. Pierre Pluye and Dr. Tibor Schuster provided helpful comments and suggestions for this chapter.

Chapter 8. Conclusion

I am the first author of this chapter. Dr. Pierre Pluye provided helpful comments and suggestions for this chapter.

CHAPTER 1: INTRODUCTION

In this thesis I will argue that the time has come for a post-marketing assessment of the impact of predicted drug-drug interactions on patient safety using real-world data. This can enhance the quality of drug-drug interaction compendia, and thus improve the quality of information that clinicians rely on to help guide their patient care decisions.

This thesis focuses on measuring the exposure to and impact of drug-drug interactions predicted to lead to adverse drug events among community-dwelling, non-elderly adults. It provides a knowledge synthesis of the prevalence of exposure to drug-drug interactions among community-dwelling, non-elderly adults in various countries around the world, followed by an estimation of the prevalence, incidence, and determinants of exposure to high-priority, drug-drug interactions among community dwelling, non-elderly adults in the Canadian province of Québec. It presents an assessment of the impact of exposure to four common drug-drug interactions on the risk of emergency department visits, hospitalizations, or death. This work was completed as part of an embedded fellowship in the Québec health care system, using routinely collected administrative databases and developing analytical resources that would allow for the routine assessment of the scientific aspect of this work in the Québec context.

Thus, the objectives of this thesis are fourfold:

(O1) To summarize the prevalence of exposure to drug-drug interactions among non-elderly adult outpatients reported in the literature (Manuscript 1);

(O2) To measure the frequency of exposure to drug-drug interactions among community-dwelling non-elderly adults in Quebec (Manuscript 2);

(O3) To identify the health service use variables that predict exposure to drug-drug interactions (Manuscript 2);

(O4) To assess if the co-exposure to known drug-drug interactions is associated with anincreased risk of an adverse event (Manuscript 3).

1.1 Rationale

The development and use of medications are a cornerstone of our health care systems, acting as the clinicians' main therapeutic tool and have allowed us to live healthier and longer lives. As with any intervention, care must be taken to ensure medication use is safe and effective. The potential for medications to lead to iatrogenic harm is increasingly recognized as a major barrier to the safety, effectiveness, and sustainability of our health care systems. [3] The increasing rates of polypharmacy across the population lead to increased risk of patients being exposed to drug-drug interactions.

Drug-drug interactions arise when the effects of a drug are altered by the effects of another drug. Drug-drug interactions can drastically change the pharmacological profile of a drug and as such are often used intentionally to optimize treatments. [4, 5] Conversely, unintentional exposures to drug-drug interactions may lead to preventable adverse drug events for patients. [3] This thesis will focus exclusively on unintentional drug-drug interactions which have the potential to lead to adverse drug events.

Adverse drug events arising from a patients' unintentional exposure to drug-drug interactions are a recognized risk among certain patient subpopulations (such as the elderly, and those living with a condition requiring complex pharmacotherapy) and in hospital settings. In contrast, data on the prevalence and impact of drug-drug interactions exposure in the primary care outpatient setting is scarce [3] yet alarming. [6] Thus, I conducted a systematic literature review and meta-analysis on the prevalence of exposure to drug-drug interactions among non-elderly adult outpatients (objective O1, Manuscript 1).

Global prescription rates have increased rapidly in recent decades and Canada is no exception with 55% and 36% of Canadian adults aged 18 to 79 using at least one or two prescription drugs in the past month, respectively.[7] In addition to high levels of prescription drug exposure, Canadians have high levels of multimorbidity, [8] and poor continuity of care as access to a regular family physician is difficult for large segments of the population. Lower continuity of care has also been shown to predict exposure to drug-drug interactions. [9] Current published efforts to improve prescribing practices in Quebec have focused on elderly (>65 adults).[10] Compared to elderly adults older than 65, non-elderly adult populations in Quebec are more likely to experience fragmented care, with 64% of adults aged 18-34 years affiliated to a family physician compared to 90% of those aged 65 or more,[11] and were more likely to report an error in their care [12].

There are currently no published studies on the frequency and impact of exposure to drug-drug interactions among non-elderly, community-dwelling adult residents in Québec, or any other part of Canada. Therefore, my empirical research measured the prevalence, incidence, and the health service use variables that predict exposure to high-priority drug-drug interactions among non-elderly adult outpatients in Québec (objectives O2 and O3, Manuscript 2).

Databases with lists of potential drug-drug interactions are widely used by clinicians. Different proprietary classifications of drug-drug interactions exist, with paid subscriptions required to access them. However, there is no disclosure of the rationale behind the classification. Furthermore, studies have shown very limited overlap between the different databases in existence. [13] Therefore, an academic, open-access source of high-priority drug-drug interactions (i.e., those with high risk of leading to adverse drug events) is urgently needed. Such a database is included as part of this thesis (Appendix 2).

A problem in the prevention of drug-drug interactions is the uncertainty about which drug-drug interactions lead to actual adverse drug events. Clinicians often override drug-drug interactions alerts and choose to expose their patients to what is often perceived as a low risk of an adverse drug event from exposure to drug-drug interactions. All new drugs must undergo an assessment of their risk for interacting with other drugs as part of their approval process. The results of these assessments form the basis for establishing lists of potential drug-drug interactions, whose predictive value for an actual adverse drug events remain uncertain.[14] The development of methods to routinely assess the impact of exposure to different drug-drug interactions is a key component of safe prescribing practices. Thus, I assessed whether administrative healthcare databases can be used to evaluate the association between risk of exposure to selected drug-drug interactions and the occurrence of an adverse event (objective O4, Manuscript 3).

1.2 Overview of the thesis

This thesis is comprised of three manuscripts. The literature review in Chapter 2 provides a detailed overview of what is known about drug-drug interactions, their classification, and the clinical tools in current use to manage the risk of exposure to drug-drug interactions (Chapter 2). The definition and typology of adverse drug events is also presented. The phenomenon of drug-induced long QT syndrome, and its relevance when assessing the impact of exposure to drug-drug interactions is described. The Canadian healthcare context in which the primary research for this thesis was conducted will be discussed, particularly with regards to the Canadian post-marketing surveillance context. The definition and impact of continuity of care on medication errors is discussed. Finally,

the pharmacological profile of the drugs of interest involved in the high-priority drug-drug interactions is investigated as part of the fourth objective of this thesis.

The methods Chapter presents details regarding the systematic literature review and meta-analysis of studies measuring the prevalence of exposure to drug-drug interactions among community-dwelling, non-elderly adults (Chapter 3). This includes the search strategy, modified checklist to appraise the methodological quality of included studies, and the proposed method for calculating 95% prediction intervals for prevalence proportions. The methods used to assess the prevalence and incidence of drug-drug interactions using administrative health databases are presented, with details regarding the assessment of overlapping drug exposures. The SuperLearner algorithm that was employed to predict the risk of exposure to a high-priority drug-drug interaction based on health system use variables including continuity of care is described. The operationalisation of continuity of care as two validated measures, the usual provider of care and the Bice-Boxerman index, are discussed. The Québec index of social and material deprivation is presented, along with the validated measure of multimorbidity used. Finally, the Cox proportional and non-proportional hazards survival analysis with time-varying drug exposures used to assess the impact of exposure to four high-priority drug-drug interactions is described. Further details on the methods used to create an open-source drug-drug interactions database and to conduct this study using provincial administrative health databases are presented in the Appendix.

The first manuscript is a systematic literature review and meta-analysis of the prevalence of exposure to drug-drug interactions (Chapter 4, Objective 1). This work revealed a high degree of methodological heterogeneity in drug-drug interaction studies, and highlighted the importance of carefully selecting and specifying the drug combinations leading to high-priority drug-drug

interactions. We propose a method to compute 95% prediction intervals for the meta-analysis of prevalence proportions, which avoids a common artifactual pitfall in their calculation.

The second manuscript consists of an estimation of the prevalence and incidence of exposure to high-priority drug-drug interactions among non-elderly, community-dwelling adults in the Canadian province of Québec, using provincial administrative health databases (Chapter 5, Objectives 2 and 3). This study also uses machine learning tools to identify the health system use variables predicting increased risk for exposure to a high-priority drug-drug interaction in this context. The results from this work will help identify the most significant areas where intervention can prevent exposure to drug-drug interactions in the patient community.

The third manuscript examines whether exposure to select high-priority drug-drug interactions leads to an increased risk for an adverse drug event. Cox proportional and non-proportional hazards models were created using time-varying drug exposures (Chapter 6, Objective 4). Three different approaches to modeling time-varying drug exposure were completed: current use, cumulative dose of past 30 days, and cumulative dose of past seven days.

With respect to appendices, a major finding of the early stages of this thesis was the large methodological heterogeneity present in studies on drug-drug interactions. While many vendors provide databases with predicted drug-drug interactions, paywalls and opacity in the methods to classify a drug pair as a potential drug-drug interaction result in an incomplete picture when reporting drug-drug interaction studies. Thus, a replicable list of high-priority drug-drug interactions from open academic sources was created as part of this thesis; this database was used in the second manuscript. The details and methods for the development of this database are presented in Appendix 2, with a primary goal to serve the scientific community interested in

assessing the impact of exposure to drug-drug interactions in a more open and reproducible manner.

This thesis was completed while the author was an embedded Health Systems Impact fellow of the National Institute for Excellence in Health Care and Social Services of Québec (*INESSS, Institut national d'excellence en santé et en services sociaux*). This embedded fellowship, granted by the Canadian Institutes for Health Research, had the dual purpose of facilitating the knowledge translation component of this thesis while fostering the fellow's professional competencies required to contribute meaningfully to the healthcare system. Part of this fellowship consisted in developing the tools and methods required to complete a regular assessment of the frequency of exposure and impact of drug-drug interactions among the community-dwelling population of Québec. These tools are presented as Appendix 4.

Potential impacts/statement of originality

The research in this thesis constitutes original scholarship and contributes to knowledge in the field of pharmacoepidemiology by (1) providing a synthesis of the studies measuring exposure to drug-drug interactions among community-dwelling, non-elderly adults, (2) measuring the extent of exposure to high-priority drug-drug interactions among non-elderly adults in Québec, (3) identifying risk factors for the exposure to drug-drug interactions using machine learning, and (4) estimating the association between exposure to selected drug-drug interactions and the risk of experiencing an adverse health outcome. The third and fourth contributions to knowledge correspond to innovative methods (Manuscripts 2 and 3, respectively). In addition, I provide a unique open-access database of high-priority drug-drug interactions using public resources, and a

method to create and maintain such a Database (Manuscript 2, supplementary material). The systematic review (Chapter 4) shows that I am the first to investigate the exposure of non-elderly community-dwelling adults to high-priority drug-drug interactions in Québec and Canada.

In manuscript 1, I present a data-based approach to compute meta-analytic prediction intervals to avoid an artifactual pitfall in their calculation. Manuscript 2 provides a detailed portrait of the exposure of non-elderly adults to drug-drug interactions. Continuity of care indicators by physician type and pharmacy were used to reveal crucial intervention opportunities to reduce patients' risk of exposure to drug-drug interaction. These opportunities for intervention can greatly decrease the amount of adverse drug effects. The use of the machine learning algorithm Superlearner allowed me to predict with high accuracy the risk of exposure to drug-drug interactions. In manuscript 3, the programing codes and analytic framework developed may be replicated with any pair of drugs predicted to lead to a clinically significant drug-drug interaction. The algorithm can be used in the routine assessment of the impact of exposure to drug-drug interactions. This novel analytical framework gives results which are meaningful and easy to interpret.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1 Definitions

In this thesis, the term drug refers to a small molecule therapeutic agent that is used with the goal of improving human health. This definition excludes biological pharmaceuticals, diagnostic agents, nutritional supplements, excipients included in therapeutic formulations, and vaccines.

The word interaction is defined by the Oxford English dictionary as "Reciprocal action; action or influence of persons or things on each other".[15] In a drug-drug interaction, two drugs interact with each other and mutually change their expected effects or exposure profile, as explained in further detail below.

The concept of interaction is also commonly used in molecular pharmacology to describe the contact between biological molecules (e.g., protein – receptor interaction), and between a drug and its target biological molecule(s). Typically, drugs require a non-covalent interaction with a biological target molecule in order to exert their desired pharmacological action. These interactions are mediated by electrostatic or hydrophobic forces and are an expected and required aspect of pharmacology.

Finally, in epidemiology and statistics, the concept of interaction is used to describe the situation where the effect of an exposure on an outcome depends on the level of another exposure; this differs from effect modification in that in an interaction both exposures are modifiable by an intervention. [16] In this context, a statistical interaction is said to occur if the magnitude of the effect of two exposures together differs from the sum of both individual effects (additive interaction), or if, on the risk ratio scale, the product of the effects of each individual exposure is smaller than the effects of both exposures considered together (multiplicative interaction).[17]

The existence of a drug-drug interaction leading to an adverse outcome can be assessed with the help of statistical models including an interaction term on the additive or multiplicative scale.[17]

Drugs have allowed us to lead longer and healthier lives. In recent decades, rates of prescription drug use by the general population have increased in concert with the aging population, the emergence of new medications, and increased multimorbidity. This rapidly evolving setting requires novel interventions to ensure the safe and effective use of medications.

Drugs are clinicians' most widely used therapeutic intervention, with 68.7% of primary care visits in the U.S. being medication-related.[18] In Canada, 55%, 36%, and 24% of adults aged 18 to 79 years used at least one, two, or three prescription drugs in the past month in 2016-2019.[7]

Iatrogenic harm is defined as harm to patients caused by medical care and is estimated to be a leading cause of death in Canada and the U.S. [19-21] Among iatrogenic harm, adverse drug events are defined as the "harm experienced by a patient as a result of exposure to a medication".[22] It is estimated that 300,000 Canadians suffer serious to fatal harm from adverse drug events each year.[23] In the U.S., an estimated 700,000 visits to the emergency department and 100,000 hospitalizations per year are due to adverse drug events.[22] While some of these adverse drug events arise in an unpredictable manner ('side-effects'), predictable and preventable adverse drug events are estimated to account for half of all adverse drug events. [22, 24]

Preventable adverse drug events arise from medication errors, which are defined as "errors (of commission or omission) at any step along the pathway that begins when a clinician prescribes a medication and ends when the patient actually receives the medication". [22] The failure to consider patients' medication regime at the time of a new prescription may lead to preventable

adverse drug events due to drug-drug interactions. Unknown and unexpected drug-drug interactions may also arise between two drugs and lead to patient harm, without the need for a medication error. Drug-drug interactions are estimated to account for approximately 22% of drug-related adverse events leading to hospitalizations, and for 0.12 – 6.3 % of all hospital admissions. [25-29]

Most prescriptions originate in primary healthcare. [30, 31] A recent systematic review reported that safety incidents involving prescription drugs and diagnostic errors in primary care were the most likely to cause severe harm to patients. [32] The improvement of drug safety was identified as a high-priority area by the National Academy of Sciences in the US since 2001, due to their high degree of preventability, burden of patient harm, and societal cost. [20] Medication errors remain a major barrier to the sustainability of health systems worldwide, according to the World Health Organisation. [3]

In this chapter, I will review the literature on the current understanding of the known mechanisms underlying drug-drug interactions, the efforts in place to prevent harm from exposure to known drug-drug interactions, the shortcomings of such efforts, and the health system and demographic factors associated with increased risk of exposure to drug-drug interactions.

2.2 Drug-drug Interactions

A drug-drug interaction between two drugs is the change in one drug's behaviour caused by the effect of another drug. The drug inducing the change is known as the perpetrator drug, and the drug whose effect is changed is considered the victim drug.[33] This terminology is widely used, even though mutual or two-way interactions may occur, where both drugs in a drug pair simultaneously act as perpetrators and victims for different drug-drug interactions.[34]

The effects induced by a perpetrator drug may change the victim drug's absorption, metabolism, distribution, and/or excretion in the case of pharmacokinetic drug-drug interactions; or they may involve the change in pharmacological action of the victim drug, for example through the biochemical interaction of victim and perpetrator drug at their site(s) of action, in the case of pharmacodynamic drug-drug interactions. [35] Both types of drug-drug interactions are discussed in further detail below. While drug-drug interactions can arise between multiple drugs simultaneously, the work comprised in this thesis focuses exclusively on drug-drug interactions between two drugs.

Drug-drug interactions may arise and lead to no clinically significant effect due to biological variability and redundancy (e.g., in metabolic pathways). Clinically significant drug-drug interactions may lead to either an amplification of the effect of one or both of the drugs, with a corresponding increase in the risk of experiencing an adverse drug event, or they may lead to decreased pharmacological effect or decreased exposure to one or both drugs, with therapeutic failure if the exposure level is beneath the minimum effective concentration for that drug.

This section will present the pharmacological basis for drug-drug interactions, followed by known examples of each type of drug-drug interaction.

2.2.1 Pharmacodynamic drug-drug interactions

Pharmacodynamic drug-drug interactions arise when the effects of two drugs change the pharmacological action of the drugs involved. [36] Pharmacodynamic drug-drug interactions may arise when the victim and perpetrator drug exert an effect on the same molecular drug target, or when their effects on different targets interact at some later point of the complex signalling networks present in biological systems.[35, 36] This joint effect may be additive or synergistic if

both drugs act in the same direction (for example, if both drugs are agonists or partial agonists at the same receptor), or may be antagonistic if the drugs exert an action in the opposite direction and the resulting effect is less than the expected additive effect of both drugs. [35, 36]

Pharmacodynamic drug-drug interactions are more common than pharmacokinetic drug-drug interactions, and are comparatively understudied. [28, 36] There is currently no systematic approach nor framework to assess the existence and magnitude of pharmacodynamic drug-drug interactions in the preclinical stage of drug development, although simulation-based approaches are under development. [35, 36]

Currently most studies assessing possible pharmacokinetic drug-drug interactions are performed using high-throughput *in vitro* screening during drug development, analysed assuming linear signaling pathways instead of the complex interconnected signaling networks with tightly regulated temporal and spatial dimensions present in biological systems. [36, 37] Among the biggest challenges in the study of pharmacodynamic drug-drug interactions is our limited understanding of the detailed mechanisms of action of drugs, which are still being elucidated. [36] This is partly because many drugs have promiscuous targets and can affect many different biological molecules. A recent comprehensive map of molecular drug targets highlighted the complexity in identifying the precise molecular targets of a drug, partly due to the promiscuity of their effects, and identified 558 different human proteins and biomolecules acting as the main therapeutic target for FDA-approved drugs (small molecule drugs only). [38] The abundance of possible drug targets, and the fact that a single drug may affect multiple biological molecules simultaneously, result in an impossibly large number of possible pharmacodynamic drug-drug interactions.

Beneficial pharmacodynamic drug-drug interactions are used in HIV therapy, hypertension management, and cancer chemotherapy. [35, 36] Unintentional and harmful pharmacodynamic drug-drug interactions have been documented, for example the elevated bleeding risk when oral glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) are taken together.[39]

2.2.2 Pharmacokinetic drug-drug interactions

Pharmacokinetic drug-drug interactions are the best understood type of drug-drug interaction, and as such their prevention has been described as the most relevant and actionable consideration in the prevention of adverse drug events. [24]

Pharmacokinetic drug-drug interactions arise when the perpetrator drug causes changes to the absorption, distribution, metabolism, and /or elimination of the victim drug, which may translate to a very different exposure profile to the victim drug involved. Pharmacokinetic drug-drug interactions are considered a major cause of adverse drug events. [35]

The pharmacological action of a drug depends on its concentration at the sites where that action takes place, which generally depends on the drug's concentration in the blood. [40] Drugs have a therapeutic range, whereby the drug is expected to exert its desired effect within a range of drug concentrations in blood; drug concentrations falling beneath the minimum effective concentration fail to exert the desired effect at a sufficient level, whereas drug concentrations exceeding the maximum tolerated concentration confer no improved therapeutic effect and place the patient at increased risk for adverse events.

Normal dosing recommendations for each drug are calculated based on the average rate of drug absorption, metabolism, and clearance observed in healthy individuals taking only one drug. [41] Pharmacokinetic drug-drug interactions can lead to dramatic changes in the blood concentration

of a drug or its metabolites, with the potential to change the blood concentration of a drug or by-product by more than an order of magnitude. [42]

Multiple mechanisms may result in a pharmacokinetic drug-drug interaction. Among the best understood, transporter-mediated and cytochrome P450 mediated pharmacokinetic drug-drug interactions are described.

2.2.3 Transporter-mediated drug-drug interactions

Transporters are specialized proteins that shuttle molecules (endogenous as well as exogenous) across cell membranes; they form the basis for tissue barriers. So far, over 450 different transporter proteins have been identified in humans; these are broadly classified into two superfamilies: ATP-binding cassette transporters, and solute carrier transporters. ATP-binding cassette transporters are generally efflux transporters which use energy to protect sensitive tissues from toxic molecules, while solute carrier transporters are usually influx transporters which mediate the uptake of nutrients. [43]

Drug-drug interactions involving one or more of these transporter proteins may lead to altered pharmacokinetics of one or both drugs involved through changes in the uptake or excretion of the drugs and their metabolites. Drugs or their metabolites may inhibit the activity of a transporter. For example, the immune suppressant cyclosporine inhibits the activity of intestinal P-glycoprotein and breast cancer resistance protein (both ATP-binding cassette efflux transporters), as well as hepatic organic anion transporter (a solute carrier transporter).[33] When an individual is exposed to both cyclosporin and lovastatin, plasma lovastatin concentrations over time (AUC) may increase by 5-20 fold, drastically changing the drug exposure and responses elicited.[43]

Drugs may also induce the expression of a transporter, increasing its activity by increasing the quantity of transporter present in the cell.[34]

2.2.4 Cytochrome P450-mediated drug-drug interactions

One of the best-understood mechanisms behind pharmacokinetic drug interactions involves the reactions of the cytochrome P450 family (CYP) of enzymes. CYP enzymes are involved in a plethora of biological processes, from mitochondrial respiration to the breakdown of toxic compounds and bioactivation of biologically inert compounds.[41] These enzymes have been extensively studied since their identification in the early 1960s because of their evident roles in drug metabolism and carcinogenesis. [44] More recently, the genetic regulation of CYP enzymes has received much attention as the basis for pharmacogenomics: genetic variations (polymorphisms) affecting CYP genes which lead to an individual's classification as an "extensive metabolizer" or as a "poor metabolizer" of certain drugs. [44] To date, 57 different isoforms of human CYP enzymes have been identified based on genomic analyses; however, their precise functional roles remain incompletely understood.

CYP enzymes are known to be involved in the bioactivation or degradation of an estimated 75% of all commercial drugs.[41] Importantly, the activity of CYP enzymes is itself very highly modulated by exposure to certain drugs. For example, carbamazepine and phenobarbital induce, while SSRI antidepressants and proton pump inhibitors inhibit the activity of some CYP enzymes; these changes in activity can be dramatic and cause major increases or decreases in the metabolic activity of different CYP enzymes, with the potential for increasing the formation of, or prolonging the half-life of, toxic metabolites or parent compounds. [28] Each CYP enzyme can potentially

affect the metabolism of multiple drugs, and multiple different drugs can affect the activity of any single CYP enzyme.

Two main types of CYP inhibition have been described: direct inhibition occurs when the drug or its metabolite directly inhibits the action of the enzyme by binding to it, whereas indirect inhibition occurs when a drug or its metabolite interferes with the normal function of the CYP enzyme by interfering with other mechanisms required for CYP activity, such as the diversion of the electron chain away from CYP.[45] The following sections deal exclusively with direct CYP inhibition.

Among CYP direct inhibitors, two main types are recognized: (1) reversible inhibitors, whereby a perpetrator drug decreases the rate of metabolic activity for a victim drug by competing for the CYP active sites with the victim drug, or through allosteric inhibition, in a concentration-dependent manner, and (2) irreversible inhibition, whereby an inhibitor drug irreversibly binds and permanently inactivates the functional CYP enzyme, requiring de novo protein synthesis to replace it, thus leading to marked and sustained loss of enzymatic activity in a concentration and time-dependent manner.[46]

Reversible CYP inhibition

This type of enzyme inhibition occurs when a perpetrator drug (or one of its metabolites) inhibits an enzyme by binding to it non-covalently with an affinity that allows for the association and dissociation of the drug-enzyme complex under physiological conditions. [46] Thus, when the perpetrator drug is bound, the CYP enzyme's activity with the victim drug is inhibited; as the perpetrator drug dissociates from the enzyme, the enzymatic activity for the victim drug is restored. The inhibitory effect and its reversal are immediate, and dependent on the drug concentrations at the active site and the affinity of the drug to the active or allosteric site in the CYP enzyme. If the

perpetrator drug binds the enzyme at the same site as the victim drug, there is competitive inhibition. Given that most CYP enzymes are promiscuous and can metabolize a variety of different drugs, any two drugs metabolized by the same CYP enzyme may be competitive inhibitors of the metabolism of the other drug by that same enzyme. [45, 46] For example, the drug theophylline, which is metabolized by CYP1A2, can reach higher plasma concentrations if administered at the same time as the drug duloxetine, which competes with it for the active site of CYP1A2. This drug-drug interaction may be attenuated by separating their administration as much as possible. [46]

Conversely, if the inhibitor binds the enzyme in an allosteric site, non-competitive inhibition occurs. A third possibility is that a drug acts as a mixed inhibitor, where it can bind to both an allosteric site and an active site; mixed inhibitors tend to be more potent. [45, 46]

Irreversible CYP inhibition (Mechanism-based inhibition)

Irreversible and quasi-irreversible CYP inhibition occurs when a drug is metabolised by a CYP enzyme, and this process creates a reactive intermediate compound which covalently binds the CYP enzyme or its heme prosthetic group and irreversibly inactivates it. [45, 46] In contrast with reversible inhibition, this type of inhibition is time dependent, with progressively higher levels of inhibition as time of exposure to the perpetrator drug increases. The only way to restore the activity of the enzyme is through its replacement via protein synthesis; thus, the activity of the CYP enzyme on the victim drug is dependent on the concentration of perpetrator drug, its affinity to the CYP enzyme's active site, and the rate of synthesis of new CYP enzyme.

2.3 Drug-Drug Interaction Prevention Efforts

2.3.1 Preclinical assessment of drug-drug interactions

The preclinical assessment of the potential of a new drug to lead to drug-drug interactions is a critical component of the drug development process.[47] Extensive *in vitro* testing is conducted to assess the potential of a new drug to lead to clinically significant drug-drug interactions.

In the United States, the Food and Drug Administration provides detailed guidance regarding the requirements for the *in vitro* assessment of pharmacokinetic drug-drug interactions. The pharmaceutical company seeking the approval of a new drug must provide evidence of the metabolic enzymes involved in the metabolism of the new drug, along with data on any inhibitory or inductive effects of the new drug on selected key cytochrome P450 enzymes. These investigations are typically conducted using human liver tissue, liver cells (hepatocytes) or recombinant human CYP enzymes expressed in different cell systems. [33, 34]

Transporter-mediated drug-drug interactions are evaluated in a similar way, with evidence required on which transporters are involved in the new drug's disposition, and any inhibitory or inductive effect of the new drug on multiple known transporters. This research is done using human cell lines expressing the transporter of interest. [33]

These *in vitro* investigations must be completed with the new drug under investigation, in addition to any known metabolites of that drug.[33, 34]

If the evidence obtained from these initial *in vitro* investigations suggests that there is a potential for a clinically significant drug-drug interaction, mathematical models can then be used to evaluate the need for clinical investigation of the drug-drug interaction. These models are physiologically

based pharmacokinetic (PBPK) models and simulations which integrate the know information on the new drug obtained from *in vitro* investigations with selected human physiological parameters to help identify the need for clinical assessment of that drug-drug interaction.[33] If the *in vitro* results and the physiologically based pharmacokinetic modelling and simulations suggest that there is low risk for a clinically significant drug-drug interaction with the new drug, clinical investigations may not be required by the FDA.[33] In Europe, the European Medicines Agency also allows the use of population pharmacokinetic analyses to assess the potential of a new drug to lead to drug-drug interactions in cases where conventional studies cannot be performed due to methodological limitations.[34] These analyses use pharmacokinetic data obtained from phase II and III clinical trials, and typically involve the use of non linear mixed effects models. These models require simplifications, assumptions, and non trivial decisions on the part of the investigators, such as how many "compartments" of the body should be considered;[33] these decisions all heavily influence the usefulness of the models for predicting the details of the drug exposure modeling and corresponding potential for causing drug-drug interactions.[34] Their development responded to a need to make population-wide conclusions based on sparse data,[33] and are valued by the pharmaceutical industry as a cost effective method to assess the potential for multiple drug-drug interactions with a new drug, with lower costs than performing a single crossover trial to assess drug-drug interactions. The usefulness of these models to predict drug pharmacokinetics and pharmacodynamics in real-world patient settings may be limited: [48, 49] one study found that none of the 16 identified published population pharmacokinetic models adequately predicted the observed pharmacokinetics of tacrolimus in a cohort of liver transplant patients.[48] Their performance in predicting drug-drug interactions is unclear.

If the *in vitro* and modeling results indicate the potential for drug-drug interactions, clinical assessment of the drug-drug interactions may be required; these typically involve a small, randomized crossover clinical trial with healthy volunteers. The effect of the new drug on the blood levels of different validated clinical substrates (acting as potential victim drugs) are evaluated. [33, 34]

When drug-drug interactions are identified, drug sponsors are required to clearly translate all their observations into therapeutic recommendations, including the potential for any drug-drug interactions on the drug's label. [33, 34]

In Canada, Health Canada must evaluate the safety, quality, and efficacy of any drugs seeking approval. Drug sponsors (usually pharmaceutical companies) must submit complete documentation supporting their application. Once all regulatory requirements are met, a notice of compliance (NOC) for the drug is issued, and a new drug identification number (DIN) is assigned. The details regarding the necessary assessment of drug-drug interactions in Canada are limited compared to those presented by the European Medicines Agency and the Food and Drug Administration. The only mention of their regulation in publicly available documents specifies that drug-drug interactions are assessed in Canada as part of the phase I clinical trials in the drug approval process, generally on healthy volunteers. Furthermore, Health Canada specifies on its Guidance document for Labelling of Pharmaceutical Drugs for human use that information regarding known drug-drug interactions should be included in the drug label as part of the prescribing information for the drug. [50]

Alternatively, a notice of noncompliance may be issued, requiring the sponsor to submit additional evidence supporting the use of the new drug. A third option exists, the notice of compliance with

conditions (NOC/c), in which additional safety data may be required from the sponsor, including safety data obtained from post-marketing surveillance of the drug;[51] drug-drug interactions leading to adverse drug reactions are considered a reportable event by Health Canada.[52]

2.3.2 Post-marketing surveillance

Post-marketing surveillance of approved drug products is an essential component of the assessment of adverse drug reactions and drug-drug interactions, mainly because rare adverse drug events require sample sizes which would be untenable in the pre-approval stage. In addition, many drug-drug interactions remain unknown, or adequate methods to assess them may not exist.[43] The most common source of post-marketing surveillance are spontaneous adverse drug event reports collected from clinicians, patients, or drug manufacturers. [53] Spontaneous adverse drug event reports are expected to account for 1-10% of actual adverse drug events. [54, 55]

Safety signals are those which can be identified from post-marketing surveillance data, which suggest a possible causal relationship between a drug and an adverse drug event which had been previously unknown.[53] Computerised methods for the detection of post-marketing safety signals have been developed. The data sources for these analyses are spontaneous adverse event reporting systems, medical literature, or electronic health data, including medical records or administrative health databases. [53]

In Canada, Health Canada's Marketed Health Products Directorate is responsible for collecting and evaluating adverse event reports for all marketed drugs in Canada. Drug manufacturers are legally mandated to report serious adverse drug events occurring in Canada or internationally to Health Canada, which then updates the risk to potential benefit of the drug. Safety signals are investigated, and summary safety reviews are published. In 2017, Health Canada received 860,000

post-marketing adverse drug reaction reports (of which 132,000 originated in Canada), which resulted in 44 summary safety reviews.[56] These safety reviews prioritize safety assessments whose result may require a label change. [54]

Among the 252 summary safety reviews available in the Drug and health product register in January 2022, four mention drug-drug interaction as the potential safety issue under investigation.[57]

The Canada Vigilance Adverse Reaction online database contains reports of Canadian suspected or confirmed adverse drug events since 1965; two-thirds of the reports in this database were made in the past decade. [58] The rate of reported adverse drug events increased by more than four times between 2009 and 2018, going from 531 to 2,173 reports per million population.[58] Half (50.3%) of the 436,985 adverse drug events reported between 2009 and 2018 included more than one drug. [58]

In Canada, there is limited attention placed on post-marketing surveillance, with regulations focusing almost exclusively on the preclinical evidence presented by the drug sponsors.[59]

When a drug was approved with a Notice of compliance with conditions, additional post-marketing safety evidence may be required. Health Canada has acknowledged that there have been difficulties and omissions in the agency's follow through with these regulatory activities.[59] A performance review in 2011 found that Health Canada had failed to adequately achieve most of its post-approval responsibilities.[54] Calls for improved resource allocation to post-marketing surveillance and increased transparency in Health Canada's safety assessments have been made before the Canadian Senate.[54]

The Drug Safety and Effectiveness Network (DSEN) was created within the Canadian Institutes for Health Research in 2009 to conduct additional post-marketing research on drug safety and effectiveness in Canada and improve the quality of the post-marketing research on drug safety in Canada. This network receives queries directly from Health Canada and provincial drug plans, and assigns their investigation to a university-based research team.[60] DSEN coordinates three Collaborative Centres focusing on observational studies, prospective studies, and on network meta-analyses. Of special interest within DSEN is the Canadian Network for Observational Drug Effect Studies (CNODES), the Active Surveillance and Evaluation of Adverse Reactions in Canadian Healthcare (SEARCH) and the Canadian Network for Advanced Interdisciplinary Methods for Comparative Effectiveness Research (CAN-AIM). The impact of DSEN-generated information on decisions made by Health Canada has to date been limited. [61]

In addition to the pre- and post-approval assessment of the potential for a new drug to be involved in a drug-drug interaction, clinicians must work to avoid exposing patients to dangerous drug-drug interactions.

A considerable interest has been placed on promoting increased detection and awareness of drug-related adverse events in Canada in recent years. In November 2014, Bill C-17: Protecting Canadians from Unsafe Drugs Act (Vanessa's Law) was approved by the Canadian Parliament, mandating hospitals to report serious drug-related adverse events to Health Canada.[62, 63] In Quebec, a CSBE report released in March 2015 detailed several factors contributing to increasing problems with prescription medication use in Quebec, such as the strong pressures from the pharmaceutical industry to expand the market, the abundance of different medications on the market, and a basic gap in pharmacological training of physicians that causes them to disregard the potential importance of interactions [64]

2.3.3 Drug-drug interaction identification in clinical settings

As mentioned above, the potential for being involved in drug-drug interactions must be described in the drug's label. This leaves clinicians and patients the challenge of avoiding those drug-drug interactions which may be harmful. This task becomes increasingly complicated with the increased number of available drugs and the increased prevalence of patients taking multiple drugs, as the number of possible pair wise combinations increases exponentially with each additional drug consumed by a patient, with the formula

$$\text{number of possible pair-wise combinations} = \frac{n^2-n}{2},$$

where *n* is the number of drugs. Thus, an individual with 5 drugs has ten possible pair-wise combinations of drugs, each of which must be assessed for the presence of a drug-drug interaction.

Computerised clinical decision support systems integrating drug-drug interaction knowledge have been developed to help guide clinicians and patients. Several databases exist which contain information regarding drug combinations predicted to lead to drug-drug interactions; these databases are often linked to clinical decision support systems to assist clinicians at the point of care.[13] A systematic review found that Micromedex® Drug-Reax is the most widely used commercial software in published studies estimating the prevalence of drug-drug interactions.[13] In Quebec, VigilanceSanté is widely used by clinician decision-support systems. Micromedex provides a ranking of the evidence for a drug-drug interactions. Moreover, both Micromedex and VigilanceSanté also rank the clinical severity of the expected interaction. Neither of these two databases provide publicly available information on the number of drug-drug interactions included, nor on the full criteria used to select drug-drug interactions for inclusion and ranking.

There currently are no standardized methods to assess the clinical relevance or degree of severity of a potential drug-drug interaction. In addition, no standard of care specifying which drug-drug interaction alerts should be presented to clinicians at the point of care.[65] Furthermore, there is little agreement between different providers of drug-drug interaction data, with low concordance in the classification of a drug pair as leading to a drug-drug interaction, and in the classification of the severity of a drug-drug interaction. [13, 66]

Drug-drug interaction alerts are very common, are perceived to lack positive predictive value for clinically significant effects and are consequently frequently ignored by clinicians. A recent study found that 95.7% and 87.3% of all drug-drug interaction and high-severity drug-drug interaction alerts respectively were overridden by the clinician; the overrides were only appropriate in 45.4% of all overridden drug-drug interaction alerts and 0.5% of overridden high-priority drug-drug interaction alerts; patient adverse events were identified in 4.3% of patients with appropriate overrides and 9.4% of patients with inappropriate overrides.[66]

2.4 Adverse drug events caused by drug-drug interactions

Adverse events, including drug-drug interactions and adverse events caused by health care management, rank among the top ten killers in the U.S. and Canada.[21, 67] In 2000, Canada had an in-hospital adverse event (AE) rate of 7.5 per 100 hospital admissions among all non-obstetric, non-psychiatric adult patients; 20.8% of adverse events resulted in death, and about half of this (9% of the total adverse events documented) were deemed preventable deaths. [21] The prevalence and impact of exposure to drug-drug interactions among community-dwelling patients is comparatively less studied, even while most prescription acts take place in primary care settings.

[30, 31] A study on the origins of adverse drug events in U.S. hospitals found that adverse drug events were three times more likely to be present on admission than to originate during the hospital stay,[68] and a recent study identified drug-drug interactions as the possible of probable cause of 5.4% of hospital admissions over one month.[29] A systematic review on the safety of primary care identified prescription and diagnostic errors as the leading cause of severe and avoidable patient harm.[32]

It is likely that the impacts of drug-drug interactions on people's health are largely underestimated. Several studies have shown that a significant proportion of patients presenting drug-related side effects and adverse events are unrecognized and thus unclassified as such by clinicians. [27, 69, 70] Some have suggested that increases in sudden deaths among some populations may be caused by unrecognized drug-drug interactions. [69] Furthermore, clinicians may erroneously attribute instances of drug-drug interactions-induced therapeutic failure to non-adherence of the patient to their medication regime. This lack of recognition of adverse drug-drug interactions might be especially true if the patient presenting the adverse drug-drug interactions is not part of a population traditionally considered at risk for them.

2.4.1 Drug-drug interactions among drugs leading to QT changes

Drug-induced long QT syndrome occurs when certain drugs affect cardiac ventricular repolarization and cause a prolongation of the QT interval in the electrocardiogram (ECG).[71, 72] Long QT syndrome increases the risk of ventricular tachycardias known as torsades de pointes, which in turn increase the risk of sudden cardiac death. Some individuals carry mutations which lead to QT prolongation congenitally; however, drug-induced long QT syndrome is much more

common than congenital long QT syndrome. [72] Drug-induced QT prolongation has been the leading cause of drug withdrawal in the past decade.

The mechanisms behind drug-induced long QT syndrome remain incompletely understood but are currently thought to be due to the action of the drug on a potassium channel encoded by the human ether a go-go gene (hERG). [71, 72] This channel contains two aromatic amino acids (tyrosine and phenylalanine), and two polar amino acids (threonine and serine), which leads to a variety of drugs effectively binding to them and blocking the channel and causing a delay in the rapid component of the delayed rectifier potassium current.[72] Thus, many different types of drugs routinely taken for non-cardiac reasons have a known or conditional risk of causing drug-induced long QT syndrome. A full assessment of the effects of a new drug on the QT interval is required by regulators in Canada, the U.S., and Europe.

Drug-induced QT prolongation usually occurs in a dose-dependent manner. Dosage limitations for drugs with known risk of QT prolongation are established in consideration of the level of QT prolongation at varying doses given to healthy subjects. Generally, a QT prolongation of ≥10 milliseconds is considered clinically significant. For example, the commonly used antidepressant drug citalopram is subject to a black box warning limiting its dose to 40 mg daily, as higher doses increase the risk of causing a clinically significant QT prolongation without providing increased therapeutic benefit.[73]

A list of all drugs approved by the FDA with known, possible, or conditional risk of leading to long QT syndrome is curated by the AZCERT Inc and available on the CredibleMeds.org website.[74]

Drug-drug interactions involving drugs with known risk of QT prolongation may arise from a variety of mechanisms. The possibility for pharmacodynamic drug-drug interactions leading to an additive or synergistic increase in QT interval has led to warnings to avoid combinations of QT prolonging drugs.[73]

Pharmacokinetic drug-drug interactions in which the victim drug has a known or conditional risk of leading to QT prolongation may result in a considerably increased risk of QT prolongation if the result of the drug-drug interaction is an increase in the blood concentration of the victim drug.

The prevention of drug-drug interactions leading to higher risk of long QT has become especially important in the post-COVID-19 pandemic world, as COVID-19 has been shown to lead to QT prolongation during the acute phase of disease, but also among recovered symptomatic and asymptomatic patients. [75, 76]

2.5 Determinants of exposure to drug-drug interactions

The risk of being exposed to a potential DDI increases for people with multimorbidity, with each additional medication prescribed [77] and with the number of different prescribing physicians seen by a patient.[78-81] Age appears to have a strong impact on the risk of exposure to DDI, but whether this is an effect independent of the multimorbidity and exposure to polypharmacy typically found in the elderly remains unclear. One study found a higher relative risk for exposure to predicted clinically-relevant DDI among adults under 65 years of age as compared to those 65 or older; [77, 82] another study found that the effect of polypharmacy on the risk of being exposed to DDI is much greater than the effect of age, but age was found to have an independent effect on the risk of being exposed to a potential DDI. [82]

Other determinants of the risk of exposure to DDI have been found in other patient populations. Gender has been found to associate with multimorbidity,[83, 84] exposure to polypharmacy[85] and exposure to potential DDI. [86] Socio-economic status is associated with multimorbidity, [84, 87] polypharmacy, [88] and the exposure to potential DDI. [88]

Continuity of care is a concept which has been in use since the 1970s [89, 90], and refers to a longitudinal relationship between a patient and their care provider, such that there exists for the patient a "central point for integration" of all health-related services. [89] While initially referring to the physician-patient relationship, it has now been expanded to consider also continuity of pharmacist care[91], and to distinguish between different types of physician continuity (e.g., total continuity of care vs. primary care continuity).[92] Higher continuity of physician care was recently found to decrease the risk of exposure to a drug-drug interaction among outpatients in Taiwan, especially among those with higher multimorbidity. [9]

2.6 Drug-drug interactions in Quebec and Canada

Several studies have been conducted assessing drug-drug interactions among the elderly in Canada and Quebec. [26, 93, 94] A study involving detailed chart reviews of elderly patients visiting the emergency department of the Montreal Jewish General Hospital in 1998 found that 31% of their sample had at least one potential drug-drug interactions. [94] No studies assessing drug-drug interactions have been found that were conducted in Canada among non-elderly adults. However, among Quebec adults with multimorbidity, a greater proportion of those under 65 years of age face errors in their healthcare as compared to those over 65. [12].

In Canada, spending on drugs has nearly tripled in the last 25 years due mostly to increases in the number of prescriptions issued, independently of the increasingly aging population and population growth.[95] In Quebec, the situation is even more extreme: Quebec spends 30% more than the Canadian average on medications, an increase largely due to increased drug volume rather than drug cost differences. A striking report from the Commissioner for health and well-being of Quebec (CSBE; Commissaire à la santé et au bien-être du Québec) in 2014 reveals dramatic increases in the annual number of prescriptions issued in recent years, whereby the number of prescriptions issued for certain drug classes more than doubled between 2004 and 2011.[64] The same report found that 84% of adults and 90% of women in Quebec consume prescription medications, with 55% consuming them regularly; among regular consumers, 72% (i.e., 40% of the total adult population of Quebec) have prescriptions for two or more drugs. [96]

Overall, 47% of Quebecers indicate that they are affected by a disease which requires pharmacological treatment. [96] A recent study conducting patient chart reviews found that the Quebec population has high levels of chronic disease and multimorbidity: among adults in primary care aged 18-44 years, 68% of women and 72% of men present multiple chronic conditions, such as hypertension and hyperlipidemia; among those aged 45-64, the prevalence of multimorbidity is 89% of men and 95% of women[97]. This high degree of polypharmacy combined with an elevated prevalence of multimorbidity places the adult population of Quebec at a significant risk for drug-drug interactions.

Another risk factor for exposure to a drug-drug interaction is fragmented health care that is poorly coordinated [81]. A 2011 survey found that in Canada, 40% of the sickest adults experienced a gap in coordination in the previous two years[98]. In Quebec, 23% of people do not have a regular family doctor[12], which places them at increased risk of relying on visits to the emergency

department to access care[99]. Among patients with multiple chronic conditions, 80% saw two or more different doctors over the course of a year[12]. In Quebec, the surveillance of drug-drug interactions is under the legal mandate of pharmacists, which could be expected to compensate for the lack of coordination seen with multiple prescribers;[64] however, 56% of non-elderly adults use more than one pharmacy to fill prescriptions, [100] complicating the detection of drug-drug interactions by individual pharmacists.

CHAPTER 3: METHODS

3.1 Objective 1: Estimate the prevalence of exposure to drug-drug interactions among non-elderly community-dwelling adults

A systematic literature review of studies measuring the prevalence or incidence of exposure to drug-drug interactions among community-dwelling adults was performed (Manuscript 1). The full protocol for this systematic review was published in the International prospective register of systematic reviews (PROSPERO: CRD42017056956).[101] The review included observational studies measuring the prevalence or incidence of exposure to drug-drug interactions among community-dwelling adults aged 19 to 64 years. Six bibliographic databases were included, and the search strategy was developed in consultation with two specialized librarians. Two independent reviewers performed the screening of titles and abstracts, full text selection, data extraction and data appraisal. The data appraisal was done using the Joanna Briggs Institute's Critical Appraisal Checklist for studies reporting prevalence data, [2] adapted to include methodological elements specific to drug-drug interactions studies.

Prevalence and rate estimates were pooled to obtain 95% prediction intervals using two recommended methods: (1) Inverse-variance estimation, using Freeman-Tukey double arcsine transformation, (2) generalized linear mixed modeling (GLMM). In addition, we employed Monte-Carlo sampling from binomial & exponential distributions, emulating 10,000 meta-analyses with the equivalent effect and sample size distribution as the original meta-analysis (parametric bootstrapping). Prediction intervals were compared to those obtained using currently recommended methods.

3.2 Objective 2: Descriptive study of the exposure to high-priority drug-drug interactions among community-dwelling, non-elderly adults residing in Quebec (Manuscript 2)

We measured the one-year prevalence and incidence of exposure to drug-drug interactions with a longitudinal cohort study using administrative health databases of the Canadian province of Quebec (estimated population in 2021: N=8,604,495).[102]

3.2.1 Population

A longitudinal cohort of community-dwelling non-elderly adults was created from Quebec provincial administrative health databases. The source population consisted of all adult resident in Quebec (approximately 5.1 million individuals).[103]

The database population consisted of approximately 1.2 million adults aged 18 to 63 on April 1, 2014 with continuous coverage under the public prescription drug plan during the three-year period between April 1, 2014, to March 31, 2017. This date range was determined because it represented the most recent complete data available at the start of the study. Continuous coverage by the public drug insurance plan was determined by the dates of eligibility contained in the drug insurance plan eligibility file of the RAMQ.

A 5% random sample of the database population was generated from the database population with help from the data management team at INESSS using a random sampler without replacement; this random selection of participants ensured a representative sample. The sample size of 5% of the population was selected based on estimates of what would provide a representative sample for the fulfilment of objective 4 while making the development of analytical codes feasible without overexerting the computational capacity of INESSS data analysis stations. The study population

contained 63,834 non-elderly community-dwelling outpatients including 6.4 million prescription drug claims.

The demographic data for this population was linked to medical billing, hospital use, and prescription claims administrative databases using an anonymized patient identifier. The cohort was prepared for this research project from administrative databases held by the Quebec public health insurer (Régie de l'assurance maladie du Québec, RAMQ) and the Quebec Ministry of Health and Social Services (Ministère de la santé et des services sociaux, MSSS).

A time-based cohort entry was used, [104] where all drug claims between April 1 2015 and March 31 2016 were investigated following a one-year covariate assessment period (April 1 2014 to March 31 2015). Individuals with two or more drug claims during this period were further examined for periods where two or more drugs were expected to overlap, based on the date of the claim and the duration of the prescription.

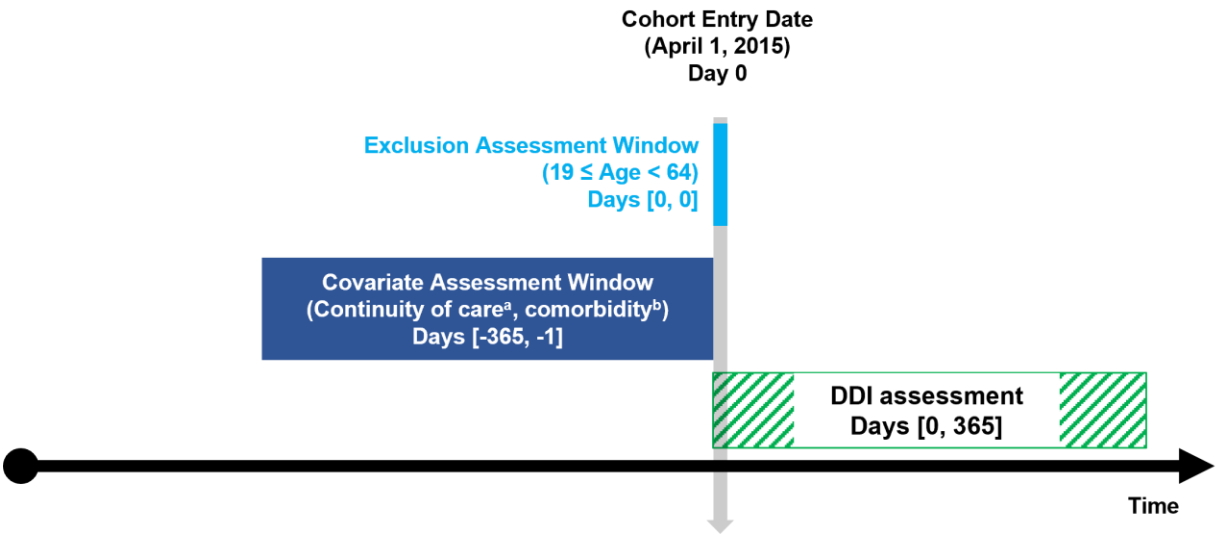

Figure 3-1. Design cohort study assessing prevalence and incidence of exposure to drug-drug interactions within periods of overlapping drugs.

Design cohort study assessing prevalence and incidence of exposure to drug-drug interactions within periods of overlapping drugs. Time-based cohort entry figure adapted from Schneeweiss et al. [104] *a.* Continuity of care was assessed using the Usual provider of care index and the Bice-Boxerman continuity of care index. *b*. Indicators for 31 chronic diseases, an index of multimorbidity predicting death and health service use, number of hospitalizations, number of medical visits, number of prescription drugs claimed at least once, number of pharmacies and number of hospital days, number of distinct prescription drugs used, number of diagnoses, and number of physician visits.

3.2.2 Data Sources

Like other Canadian provinces and territories, the province of Quebec administers its own public health care insurance plan. Under the Canada Health Act, Quebec residents are entitled to medically necessary health services without paying out-of-pocket. [105] The RAMQ and MSSS administer the health and public drug insurance plan in Quebec and maintain billing databases for these purposes. The data for each beneficiary is linked across databases through an anonymized patient identification number. The data for objectives 2 to 4 of this thesis was obtained from the administrative databases held by the RAMQ and MSSS and accessed through the National Institute for Excellence in Health and Social Services (INESSS).

RAMQ demographic database

The demographic data for the cohort was obtained from the RAMQ demographic database (fichier des bénéficiaires), with help from the drug insurance plan eligibility data to select individuals with continuous coverage under the public drug insurance plan. Each individual's anonymized unique identifier, sex, date of birth, date of death, and index of social and material deprivation were extracted.

RAMQ public drug insurance claims database

The public drug insurance claims database contains the details for each instance of a prescription drug product purchased by an individual covered by the public prescription drug insurance plan of Quebec. Permanent residents of Quebec are legally required to have some form of prescription drug insurance since 1997. [106] Those without eligibility for a private drug plan through employment or family must be covered by the public drug insurance plan and must pay an annual premium through their income tax return. [107] Thus, the public drug insurance plan of Quebec includes independent workers, unemployed individuals, recipients of last resort financial assistance, the children under age 18 whose parents are covered, and individuals aged 65 and older. The public drug plan excludes Cree, Inuit, and Naskapi permanent residents of Quebec who are insured under another program, such as the James Bay and Northern Quebec Agreement. The public drug plan also excludes individuals residing in long-term care centers and residential facilities, and does not include drugs dispensed to hospitalized individuals. [108] A file containing periods of eligibility for the public drug insurance plan is also maintained.

In the fiscal year between April 2018 and March 2019 a total of 1,268,937 adults aged 18-64 were covered by the public drug insurance plan, representing approximately 24% of the overall population of Quebec in that age group.[109]

The public drug insurance plan covers drugs included in the RAMQ medication list. The inclusion of drugs in this list is determined by Quebec's Minister of health and social services in consultation with Quebec's National Institute for Excellence in Health and Social Services (INESSS). To be covered by the public drug insurance plan, the drugs in the medication list must be prescribed by a health professional and purchased in Quebec from a pharmacist.[110]

The RAMQ public drug insurance claims database is maintained for pharmacist billing and remuneration purposes. Each record on the database contains the data on a claim for a single prescription drug product purchased by a community-dwelling individual covered by the public drug insurance plan. The date of each claim, the amount of drug product dispensed, the duration of the prescription, the drug strength code, the drug form, an active ingredient code and name, a code for the American Hospital formulary service (AHFS), and a drug identification number assigned by Health Canada (DIN) were extracted. Anonymized identifiers for the pharmacy where the claim was completed, for the dispensing pharmacist, and for the prescribing physician associated with each claim were also included with each drug claim, including the specialty of the prescriber.

RAMQ Medical Services database

All medically necessary health services are available to Quebecers on a prepaid basis. Physicians in Quebec are mostly remunerated on a fee-for-service basis. Each medical service rendered to a patient is recorded in the RAMQ medical services database, along with data describing the medical service. For this thesis, the patient identification number, the physician identification number, the physician's specialty, the date of the service, the diagnostic code associated to the service, and a code identifying the type of establishment where the medical service took place were extracted from the medical services database.

MSSS MED-ÉCHO hospitalization database

The Quebec hospital discharge database (*Maintenance et exploitation des données pour l'étude de la clientèle hospitalière,* MED-ÉCHO) contains data on all admissions to an acute care hospital in Quebec. The patient identification code, date of admission, date of arrival at the emergency

department, type of care given (e.g., day surgery, acute care), type of admission (e.g., urgent, obstetric), main diagnostic associated with the admission, and the date of discharge were extracted. The data contained in this database has been found to be accurate and comprehensive.[109] Hospitalizations coded as day surgeries (MED-ECHO variable *type de soins* code 27) and non-urgent procedures were excluded (MED-ECHO variable *type d'admission* code 3).

MSSS BDCU emergency department database

The emergency department database (*Banque de données communes des urgences, BDCU*) provided data on all visits to an emergency department. The data extracted included the patient identification number, the date of arrival at the emergency department, and the date of departure.

MSSS GMF/GRL Enrolment with a family physician or family medicine group database

Quebec's primary care model encourages enrolment of each person with a specific family physician who is responsible for their care. This family physician provides most health care needs and the necessary referrals to specialist physicians. The Ministry of Health and Social Services maintains a database with the relationships between patients and family physicians, including the dates specifying patients' periods of enrolment with different family physicians.

3.2.3 Validity of Quebec administrative health databases in health research

The RAMQ public drug insurance claims database has been used for pharmacoepidemiological research, and has been shown to be a complete and accurate means of assessing drug exposure. [111] According to a detailed assessment done by Tamblyn and colleagues, 89% of records accurately identified the drug product and prescribing physician, 69.1% matched the quantity of drug product dispensed, and 72.1% matched the duration of prescription. Most (88%) of the

inaccuracies in the duration and quantity prescribed indicated a lower duration or quantity compared to what was prescribed. Tamblyn and colleagues speculate that these inaccuracies arise from pharmacists splitting longer durations of prescription into smaller periods to better monitor patient adherence, reduce oversupplies of drugs which could be abused, and reduce financial penalties for supplying more than 30 days of drugs. [111] If this speculation is correct, then the identified inaccuracies with respect to what was prescribed by the physician may accurately reflect what was dispensed to the patient, and thus accurately represent their drug exposure patterns.

3.2.4 Variables

All drug products were assigned a unique active ingredient identifier. Different salts of the same active ingredient were grouped together. Drug claims containing only a medical device without a drug (e.g., a syringe), those containing topical drug formulations, or if those containing only vitamins or nutritional supplements were excluded.

Assessment of drug exposure

The first claim for each patient in the study period was considered to be the first date of drug intake for each patient. Each individual was assumed to be exposed to the drug dispensed for the duration specified in the claim.

Oversupplies of drugs (i.e., the overlapping over time of the same active ingredient) were carried forward such that the start of the second purchase was only consumed when the quantity initially purchased ran out. Carrying drug oversupplies (also known as stockpiling) is considered representative of real behaviour that may arise as a refill is done while there was remaining

medication from the previous refill (3, 4). Oversupplies of each individual active ingredient were carried forward if they were for an identical dose of the same active ingredient and allowed to fall outside of the observation window. If the oversupply included different doses of the same drug, claimed on the same date and for the same duration, the apparent oversupply were assumed to be intended for dose combination, and the drug strengths were added. Conversely, if the apparent oversupply included different doses and durations, where the lower dose had a shorter duration, they were assumed to be indicative of a dose ramp-up and thus carried forward. Only drug doses expected to happen within the observation window were counted (4).

A SAS program was used to adjust the expected coverage periods based on the dispensation date and duration of prescription.

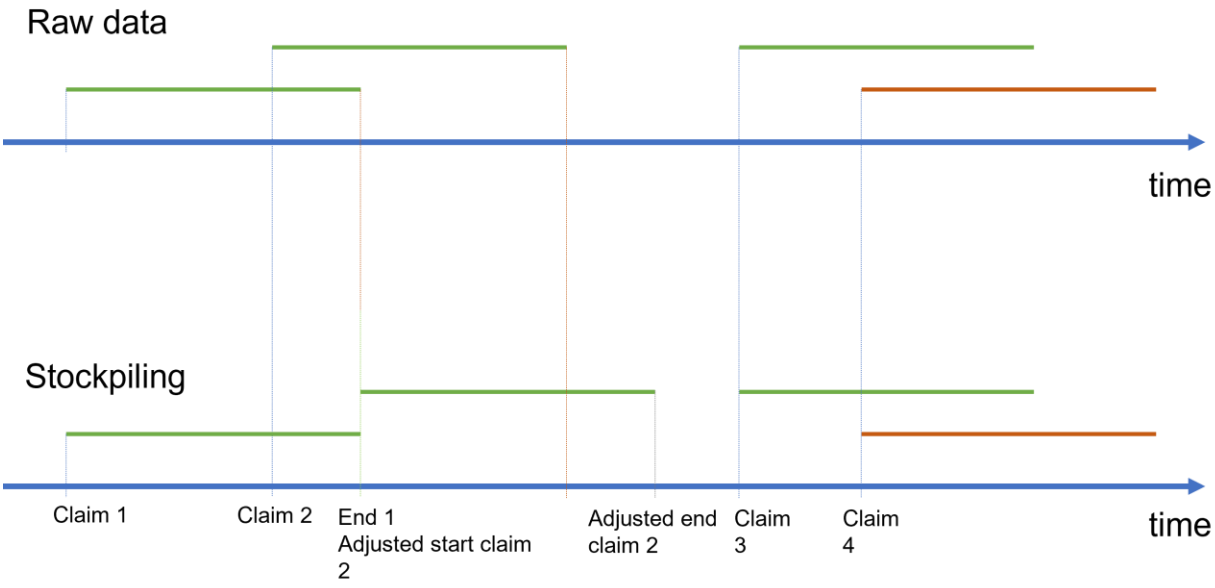

Figure 3-2. Stockpiling and Date Adjustment

Assessing exposure to drug-drug interactions

The periods of overlapping drugs for each patient were identified. All drug pairs with at least one day of temporal overlap for an individual were assessed for the presence of drug-drug interactions.

The list of high-priority drug-drug interactions from the office for the national coordinator for health in the U.S. [112] was used to create a database of drug-drug interactions with the help of the open Canadian resource DrugBank. [113] Further details on the methods followed can be found in Appendix 2.

3.2.5 Analytical methods

The one-year prevalence of exposure to drug-drug interactions was estimated using the base cohort described above. All individuals exposed to at least one day of overlapping drug exposures containing at least one drug-drug interaction were counted as prevalent cases.

The one-year incidence of exposure to any drug-drug interaction was also assessed. The first exposure to any drug-drug interaction was considered incident if the individual was not exposed to any drug-drug interactions during the 12-month covariate assessment period (April 1 2014 to March 31 2015).

Drug co-exposure patterns

We used a network analysis approach based on frequent itemset mining methods[114] to analyse the drug combinations involved in the most prevalent DDI (top 10^{th} percentile) based on the number of people exposed. The frequency of each drug combination was calculated as the number of exposed days per person.

The spectrosome shows co-exposure to the drugs involved in the most prevalent DDI. Each drug is represented by a node, each connected to the drug(s) found in co-exposure with it; colors indicate co-exposures predicted to lead to a DDI, and size indicates the proportion of person-days with drug overlap. The co-exposure tree shows the variety of DDI beyond pair-wise combinations. The heatmap shows the relative frequency of the drugs and their combinations according to the number of drugs involved.

3.3 Objective 3: Prediction of exposure to drug-drug interactions among community-dwelling, non-elderly adults residing in Quebec (Manuscript 2)

Using the same population and setting as in Objective 2, we used an ensemble machine learning approach to predict any exposure to drug-drug interactions during the one-year study period based on health service use, continuity of care, multimorbidity, demographic, and medication use during the covariate assessment period.

3.3.1 Variables

Using the data sources described in Objective 2, we extracted variables related to demographic information, prescription medication claims, medical services use, and hospital admissions and used them to measure age, sex, social and material deprivation index,[115] medication use during washout period, continuity of medical care by physician type[92] (overall, family physician), continuity of prescriber, continuity of pharmacy care (by pharmacy and by pharmacist),[116] number of hospitalizations, and multimorbidity (presence of 31 chronic conditions and a comorbidity index predictive of 30-day mortality[117]), as described below. All variables were measured during the study period.

Continuity of care: Continuity of care is important in the prevention of drug-drug interactions. [9] Guo et al. found that the risk of exposure to drug-drug interactions decreased by 3% with every 0.1 unit increase in continuity of care. [9] Multiple approaches for measuring continuity of care have been proposed.[92]

Two measures of continuity of care were used in this thesis. The usual provider of care index (UPC) is a measure of density, and the Bice-Boxerman continuity of care index (COCI) is a measure of dispersion.

The UPC was calculated as follows: (15)

$$UPC = \frac{n_j}{N},$$

where n_j is the number of visits to the pharmacy with the most dispensations during the continuity assessment period, and N is the total number of visits to all pharmacies during the continuity assessment period, measured by the number of unique dates for prescription claims during the continuity assessment period.

The Bice-Boxerman continuity of care index (COCI) was calculated using the formula

$$\text{COCI} = \frac{\sum_{i=1}^{k} n^2 - N}{N(N-1)},$$

where k is the number of different healthcare providers the patient has seen, ni denotes the number of contacts with the i-th healthcare provider and N is the total number of contacts.

Comorbidity: an index of comorbidity consisting of a combined Charlson and Elixhauser index predictive of one-year mortality and validated with Quebec administrative health databases was used. This included binary indicators for the presence of 31 common chronic conditions, the total number of conditions experienced by a patient, and a comorbidity index predictive of 30-day and one-year mortality. [117, 118]

Medical visits outside of hospitalization episodes. Medical visits billed in a fee-for-service modality appear in the medical acts database. Multiple medical acts can be billed within a single medical visit. We defined one medical visit as that occurring between one physician, one patient, on the same day regardless of the number of acts billed during the visit. The number of medical visits during the covariate assessment period was recorded.

FP enrolment. Two indicators of enrolment with a family physician were included: a binary indicator of any enrolment with a family physician recorded for at least one day during the baseline assessment period, and a proportion of the baseline assessment period during which the individual was affiliated with a family physician. All count and continuous variables were standardized.

Outcome

Individuals were considered exposed to a prevalent drug-drug interaction if during the one-year study period they were exposed to at least one day of overlapping exposure between two drugs predicted to lead to a high-priority drug-drug interaction, as defined in Objective 2.

3.3.2 Analytical methods

The SuperLearner (SL) package from R was used.[119] SuperLearner chooses the optimal weighted combination of machine learning algorithms to predict an outcome. As recommended

for binary outcomes with low prevalence, [120, 121] the SuperLearner was trained using the method of maximization of the area under the receiver operator curve (method = AUC), which represents the probability that a randomly drawn positive sample will be assigned a higher score by the trained SuperLearner than a randomly drawn negative sample.[122] A variety of algorithms were applied to maximize the likelihood of finding a good model.[120] All models were trained on 75% of the data, and a holdout sample containing 25% of each dataset was used to assess model performance, which was measured through the AUC of each model. A measure of variable importance based on the ROC curve analysis for each predictor was performed using the function filterVarImp from the Caret package. [123]

A ten-fold external cross validation of the full population SuperLearner was performed. Cross validation of subgroup SuperLearner was not done due to the excessive computational requirements for the cross validated SuperLearner.

Table 3-1. Machine learning algorithms used

Algorithm	Description	Details
Glmnet v. 4.0-2[124]	Logistic regression with Least Absolute Shrinkage and Selection Operator (LASSO)	Family = binomial; Alpha = 1; lambda = 100
RPart v. 4.1-15[125]	Recursive partitioning and regression trees	Method = class; minsplit = 20, cp = 0.01, maxdepth = 30
Random Forest v. 4.6-14[126]	Breiman's random forest algorithm for classification	1000 trees, nodesize = 1, mtry = 14
Ranger v. 0.12.1[127]	Fast random forest algorithm for high dimensional data	500 trees, nodesize = 1 mtry = 14
XGBoost v. 1.3.2.1[128]	Extreme gradient boosting	Binary:logistic, max depth = 4, eta = 0.1
Mean	Marginal mean of the outcome (prevalence or incidence of DDI)	

3.4 Objective 4: Association between exposure to drug-drug interactions and visits to the emergency department, hospitalization, or death

To assess whether exposure to specific drug-drug interactions is associated with increased hazard of an adverse event, we conducted survival analysis with time-varying drug exposures. A longitudinal cohort study was conducted using the same cohort as in Objectives 2 and 3. The study period extended for up to two years from April 1, 2015, to March 31, 2017, and the baseline assessment period covered between April 1, 2014, and March 31, 2015. Figure 3-3 shows the study design.[129]

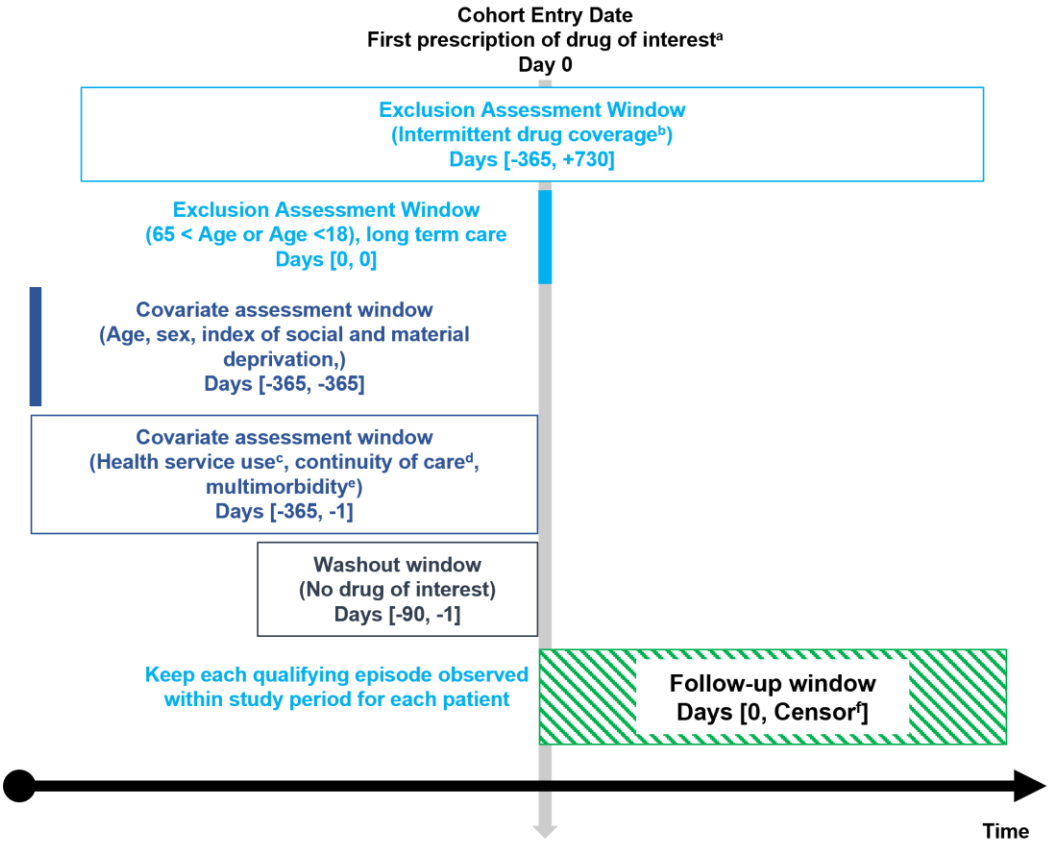

Figure 3-3. Graphical depiction of study design to measure the association between exposure to drug-drug interactions of interest and an adverse event

Time-varying modeling of drug exposure. (Adapted from Schneeweiss et al. 2019 figure "Exposure-based cohort entry where the cohort entry date is selected after application of exclusion criteria"). [104]

3.4.1 Population

An exposure-based cohort of individuals exposed to a drug involved in one of four high-priority drug-drug interactions was created from the study population used in Objectives 2 and 3. Individuals were followed from the first day of exposure to one of the drugs of interest for up to two years, until the first of an adverse event or the study's end. Only individuals who were not exposed to the DDI of interest in the 90 days washout period preceding the index drug exposure were included in the analysis.

3.4.2 Variables

Age, sex, index of social and material deprivation,[115] index of comorbidity,[117] and enrolment with family physician, as described in Objective 3, were measured during the covariate assessment window.

Each drug's strength information was verified with the help of the drug identification number (DIN) and Health Canada's drug product database. The drug strengths were converted to defined daily doses (DDD)[130] as per world health organization recommendations, using the amount dispensed and duration variables found in the prescriptions claims database.

DDI investigated

I investigated four potential DDI involving proton pump inhibitors (esomeprazole, pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole.) as the perpetrator drug, with the following victim

drugs: (1) citalopram/escitalopram, (2) domperidone, (3) quetiapine, and (4) ciprofloxacin. An individual was considered exposed to one of the four DDI of interest on any given day if the product of the doses of the two drugs involved in each DDI was larger than zero. These four drug-drug interactions were selected for this study based on their high prevalence (as found in study 2) and classification as a high-priority DDI due to their documented risk for leading to long QT syndrome.

The drug-drug interactions included in this study are described in Table 3-2.

Table 3-2. Drug-drug Interactions investigated

Drug-drug interaction	**Mechanism**
Proton pump inhibitors + citalopram or escitalopram	Inhibition of CYP2C19 can lead to decreased clearance of citalopram or escitalopram and their metabolites, potentially increasing the risk of clinically relevant drug induced long QT syndrome. Co-exposure to citalopram/escitalopram and a drug known to inhibit CYP2C19 is known to lead to higher blood levels of citalopram/escitalopram and increase the risk of long QT and torsades de pointe.
Proton pump inhibitors + domperidone	Inhibition of CYP3A4 by proton pump inhibitors may lead to decreased clearance of domperidone and its metabolites,[131] potentially increasing the risk of clinically relevant drug induced long QT syndrome
Proton pump inhibitors + quetiapine	Inhibition of CYP3A4 by omeprazole may lead to decreased clearance of quetiapine and its metabolites,[131] potentially increasing the risk of clinically relevant drug induced long QT syndrome
Proton pump inhibitors + ciprofloxacin	Proton pump inhibitors are not expected to affect ciprofloxacin metabolism.[131] Whereas ciprofloxacin is known to induce long QT syndrome,[74] no interaction between proton pump inhibitors was expected.

Proton pump inhibitor omeprazole, the first approved proton pump inhibitor, is a known mechanism-based inhibitor of CYP2C19.[46] This type of inhibition is irreversible and time-

dependent, with higher levels of inhibition occurring with prolonged exposure to the inhibitor. Only replacing the inactivated enzyme with newly synthesized protein can restore the lost activity.[45, 46] Other proton pump inhibitors have been found to inhibit CYP2C19 with varying affinities. [132, 133]

The combination of proton pump inhibitors and citalopram/escitalopram is predicted to lead to changes in the blood concentration over time of citalopram or escitalopram.[131] Recent studies have found an increase in blood levels of citalopram and escitalopram[134] and increased risk of cardiovascular adverse events[135, 136] when taken in combination with proton pump inhibitors.

Outcome

A composite outcome for adverse events was constructed, including any visit to the emergency department, hospitalization, or death. Only the first outcome was counted per person.

Hospitalizations for day surgeries and non-urgent admissions were excluded.

3.4.3 Analytical methods

Exposure to the drugs of interest and corresponding drug-drug interaction was modeled using three different definitions of time-varying drug exposure: current dose, cumulative dose in the past 30 days, and cumulative dose of past seven days.

I used the SAS (9.4) procedure PHREG with the Cox proportional and non-proportional hazards models with time-varying drug exposure were used to assess the association between exposure to a drug-drug interaction of interest and an adverse event. Dose-specific linear equations were used to compute expected hazard ratios and corresponding 95% confidence intervals at various drug

doses. The R package ‘pheatmap’[137] was used to create heatmaps presenting the hazard ratios and 95% confidence intervals at each dose of interacting drug.

Using the current use models, I used the resulting hazard ratios to approximate the daily risk ratio of an adverse event upon exposure to each drug alone and in combination with the interacting drug. This allowed me to compute the multiplicative interaction[17] using the formula:

$$\frac{HR_{DDI}}{HR_{Victim} \times HR_{perpetrator}}$$

If the value obtained from this calculation is larger than one, there is evidence of multiplicative interaction.[17]

CHAPTER 4: Frequency of exposure to potential drug-drug interactions among community-dwelling, non-elderly adults: A systematic literature review and meta-analysis of observational studies (Manuscript 1)

4.1 Preface

Drug-drug interactions are a known source of harm for certain populations, such as elderly or patients living with chronic illness. The proportion of people among the general adult population exposed to multiple medications simultaneously has increased in recent years, as have rates of multimorbidity among the general population.[1-4]

I conducted a preliminary literature review to answer the following question: what is the prevalence or incidence of exposure to potential DDI among the non-elderly, community-dwelling population? I found that few DDI studies have been conducted among the general adult outpatient population, as others have reported;[5, 6] none of these studies were conducted in Canada. The results varied widely and included multiple study designs and sources.

Thus, as a first step for investigating the frequency and impact of exposure to drug-drug interactions in Quebec, we conducted a systematic literature review and meta-analysis of the prevalence and incidence of exposure to drug-drug interactions among community-dwelling non-elderly adults. I developed a search strategy in consultation with two specialized librarians to ensure I captured as many relevant studies as possible and followed Cochrane guidance for systematic literature reviews and meta-analyses, including independent study screening, selection and data extraction. [7] This work allowed us to conduct a comprehensive descriptive synthesis of the existing literature, including of the methods used in the studies.

Frequency of exposure to potential drug-drug interactions among community-dwelling, non-elderly adults: A systematic literature review and meta-analysis of observational studies

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4.2 Abstract

Background: Exposure to drug-drug interactions (DDI) can lead to adverse drug reactions, a recognized risk among certain patient groups such as elderly patients. There is scarce evidence on the frequency of exposure to DDI among non-elderly community-dwelling adults.

Objectives: To estimate the prevalence and rate of exposure to DDI among non-elderly adult outpatients.

Data sources: Medline, Embase, BIOSIS, CINAHL, International Pharmaceutical Abstracts, and the Cochrane Library.

Study eligibility criteria: All empirical studies measuring the frequency of exposure to DDI among non-elderly outpatients and presenting age-stratified frequency of DDI.

Study appraisal and synthesis methods: Included studies were appraised using a specialized checklist on risks of bias of observational studies. Meta-analyses were conducted to pool prevalence and rate of exposure to DDI. Subgroup analyses by predefined study characteristic, e.g., reference source of predicted DDI, were conducted.

Results: The search yielded 5,449 records. Twenty-eight studies were included in the descriptive synthesis. Twelve studies reported the proportion of non-elderly adult outpatients exposed to DDI among those exposed to two or more drugs and were included in the meta-analysis. The pooled prevalence of exposure to DDI among adults exposed to two or more drugs was 0.18 (95% CI 0.09 – 0.35; PI 0.01 – 0.80); the pooled rate of exposure to at least one DDI of these same studies was 20.12 DDI per 1,000 person-months exposed to two or more drugs (95% CI 7.25 to 55.84 DDI per 1,000 person-months, PI 0.57 – 152.07).

Limitations and conclusion: Meta-analyses were limited by the clinical, methodological and statistical heterogeneity of included studies. Our results suggest that non-elderly outpatients' exposure to DDI varies widely across different settings.

Registration number: PROSPERO: CRD42017056956

4.3 Introduction

Drug-drug interactions (DDI) arise when the expected effects of a drug are altered due to the effect of another drug. Unintentional DDI can lead to adverse drug reactions (ADR) and patient harm. ADR are defined as "harmful or unpleasant reactions"[8] that result from the use of a drug and may be prevented or treated through changes in the dosage or use of the drug. ADR arising from patients' exposure to DDI constitute a well-recognized risk among elderly populations, institutionalized patients, and certain chronically ill patients with complex pharmacotherapy.[9, 10] In these populations, DDI are estimated to account for approximately 20% of ADR,[9, 11] and from 1.1% to 8.3% of all hospital admissions among the elderly population.[11-13]

In contrast, little is known about the frequency of exposure to DDI among community-dwelling non-elderly adults aged 18-64 years (hereafter non-elderly outpatients). In recent decades, this group of people is increasingly exposed to polypharmacy, as pharmacotherapy shifts to lifelong preventive and chronic disease treatments.[14, 15] To our knowledge, no systematic literature review has yet quantified the prevalence of exposure to DDI among non-elderly outpatients. Thus, the present systematic review is aimed to estimate the prevalence and rate of exposure to DDI among non-elderly adult outpatients,[16] and explore how much variability in the estimates can be explained by methods used in included studies.

4.4 Methods

This systematic review was conducted in accordance with the principles established in the Cochrane Handbook for Systematic Reviews of Interventions [17] and the Joanna Briggs' Institute guidance for systematic reviews of observational epidemiological studies reporting prevalence

data.[18] This article is presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19]

4.4.1 Protocol and Registration

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42017056956).[20]

4.4.2 Eligibility Criteria

All empirical observational studies measuring the prevalence, incidence proportion, or incidence rate [16] of DDI exposure among non-elderly adult (aged ≤ 64) outpatients were included when the age-stratified frequency of DDI was reported such that the prevalence among non-elderly outpatients could be obtained separately from the prevalence of DDI among elderly (≥65 years). Studies including youths aged ≤18 grouped with adults aged ≤64 were retained. There were no restrictions regarding publication year or language (abstract in English had to be available). Studies were excluded if the patient population included only elderly patients (≥65 years), only youths under 18 years old, or only patients hospitalized or institutionalized (long-term care, nursing home or prison). Studies were excluded when they did not define DDI exposure, did not disclose the methods used to assess exposure to DDI, or did not provide the reference source of information used to classify a drug combination as a DDI, e.g., DrugBank.[21] Given that our objective was to estimate the burden of DDI faced by all non-elderly outpatients, studies were excluded if they pertained to one specific condition (e.g., diabetes) or focussed only on a specific treatment. Studies that included non-elderly outpatients but did not provide age-stratified prevalence or incidence outcomes were kept and authors were contacted to request additional data.

4.4.3 Information Sources

Studies were identified by searching relevant electronic databases through Ovid, with no limits on the date or language of publication. The databases searched were Medline (1946-2018), Embase (1947-2018), BIOSIS (1969-2018), CINAHL (1937-2018), International Pharmaceutical Abstracts (1970-2018), and the Cochrane Library (1996-2018). The last search was conducted on October 30, 2018. The reference lists of identified eligible studies were hand searched for additional records.

4.4.4 Search Strategy

The search strategies were developed in consultation with two specialized librarians using a combination of free-text terms and database-specific thesaurus terms. We included terms relating to the subject (drug-drug, and interaction of drug or medication or medicine or prescription or pharmaceutical), the type of outcomes (prevalence and incidence), the study designs (retrospective, prospective, cohort, cross-sectional, health surveys), and the population of interest (non-elderly outpatients). A filter excluded studies focusing on infants, children, or adolescents. Studies were automatically excluded when their title included terms related to children or elderly patients, or if they focused on drug interactions with only one specific drug (e.g., Warfarin) or one specific condition (e.g., cancer). The full search strategy for Medline is included in the supplemental material.

4.4.5 Study Selection

Assessment of the studies for eligibility was carried out independently by two reviewers (QNH and AGR) using standardized forms in DistillerSR (Evidence Partners, Ottawa, Canada). Titles and abstracts of identified records were screened by both reviewers. Any disagreements were

automatically included for full-text review. Full-text reviews for eligibility were also performed independently by the same two reviewers, and disagreements were discussed until consensus was reached.

4.4.6 Data Extraction

A data extraction form was created and pilot-tested using five eligible studies. Two reviewers (MP and AGR) independently extracted the data from all included studies. Disagreements were solved by a third reviewer (QNH). Additional study details were requested from authors as needed. From all included studies, data were extracted according to general characteristics and the specific types of study methods. General characteristics were: (a) the year(s) in which the study was conducted; (b)the duration of the study period; (c) the country where the study was conducted; (d)the setting (population-based vs. hospital outpatient clinic vs. primary care clinic); (e)the study design (cross-sectional or longitudinal); and (f)the participants' characteristics (population under study, participant eligibility, definition of population at risk (whole population or those with two or more prescriptions), participant demographics, including the age ranges of adults included in the study). In addition, the types of study methods were: (a)the source of data used to infer patterns of drug use such as dispensed drugs, patient interviews, chart review or electronic medical records; (b)the definition of DDI exposure, i.e., concomitant claims or prescriptions, and temporal overlap between two drugs, claims or prescriptions over a fixed period; (c)the source of information used to identify interacting drug combinations; (d)the number and type of DDI included, e.g., all vs. clinically significant only; and (e)the frequency of DDI including the number of patients exposed to DDI, number of patients included, number of patients at risk, number of prescriptions considered, number of prescriptions including at least one DDI, and total number of DDI considered.

4.4.7 Risk of bias in individual studies

All included studies were independently assessed by two reviewers (AGR and QNH) using the Joanna Briggs Institute's Critical Appraisal Checklist for studies reporting prevalence data.[18] For each item in the checklist, methodological elements pertaining to DDI studies were specified (supplemental material Table S5).

4.4.8 Summary Measures

The primary outcomes of interest were the 95% prediction intervals (PI)[22] of the prevalence and rate of exposure to DDI among adults exposed to two or more prescription drugs, calculated using generalized linear models. This outcome was calculated using two measures of occurrence:[16]

1) *Prevalence*. We considered the proportion of individuals exposed to at least one DDI out of all adults exposed to at least two drugs during the study period. The number of individuals exposed to at least one DDI in each study was recorded as raw counts, as was the number of people exposed to at least two drugs.

$$Prevalence = \frac{Number\ of\ adults\ exposed\ to\ \geq 1\ DDI}{Number\ of adults\ with\ \geq 2\ drugs}$$

2) *Rate*. To account for varying study durations, the relative rate[16] of DDI exposure was also approximated for each study as:

$$DDI\ exposure\ rate = \frac{Number\ of\ adults\ exposed\ to\ \geq 1\ DDI}{(Number\ of adults\ with\ \geq 2\ drugs) \times study\ duration\ (months)}$$

This analysis assumes that all individuals in each study were followed for the entire study duration, and that the participants' risk of exposure to DDI was uniform across participants and throughout the duration of follow up in each study.

4.4.9 Synthesis

Generalized linear mixed models (GLMM) were used to pool prevalence and rates and compute 95% PI for each outcome.[22] Prevalence estimates were meta-analysed using a random intercept logistic regression model; [23, 24] individual study 95% confidence intervals were computed using the method of Clopper-Pearson and maximum likelihood estimation of the between-study variance; adjustment of the model was performed using the method of Hartung-Knapp. The function 'metaprop' with GLMM from R (version 3.5.1) package 'meta' was used.[25] In addition, we conducted a random effects meta-analysis, using the Freeman-Tukey double arcsine transformation as recommended for meta-analysing prevalence estimates.[26]

The rates of exposure to DDI were meta-analysed using a random intercept Poisson regression model.[22] The function 'metarate' with GLMM from R package 'meta' was used.[23, 25]

In addition, we employed Monte-Carlo sampling from binomial & exponential distributions, emulating 10,000 meta-analyses with the equivalent effect and sample size distribution as the original meta-analyses of prevalence and exposure rates (parametric bootstrapping). PI were compared to those obtained using currently recommended methods.

In addition to PI, estimates from studies presenting the same outcome were assessed for heterogeneity using the Tau-squared statistic (τ^2).[27, 28] We conducted subgroup analyses according to pre-specified study characteristics: types of DDI included (all vs. clinically significant only), source of data to assess drug exposure (prescriptions issued vs. prescriptions dispensed vs.

current use assessed by patient interview), and temporal DDI definition (inclusion of overlap vs. none).

4.4.10 Assessment of reporting bias

Funnel plots were built for prevalence estimates using sample size of the studies on the Y-axis, and the log odds of exposure to DDI on the X-axis, as recommended for meta-analyses of proportions.[26]

4.4.11 Additional analyses

Subgroup analyses by the predetermined methodological choices: type of DDI (all vs. clinically relevant only), source of data to asses drug exposure (prescriptions issued by a healthcare provider vs. dispensed or claimed prescriptions), and assessment of DDI within temporally overlapping or concurrent drugs (yes vs. no) were conducted for both prevalence and rates of exposure to DDI.

4.5 Results

4.5.1 Study selection

The PRISMA flowchart is presented in Figure 1. Database searches resulted in 6,537 records, which became 5,449 after duplicates were removed. Of these, 355 studies were selected for full-text screening. Sixty-two articles were eligible for inclusion. Six additional records were identified through hand searching the references of eligible studies, bringing the total number of eligible records to 68. Of these, 27 publications corresponding to 28 studies presented an age-stratified prevalence of DDI, such that the prevalence among non-elderly outpatients could be obtained separately from the prevalence of DDI among elderly (≥ 65 years). Of the 28 included studies, 12

presented enough data to calculate the prevalence as defined in this synthesis and were included in the meta-analysis (main synthesis).

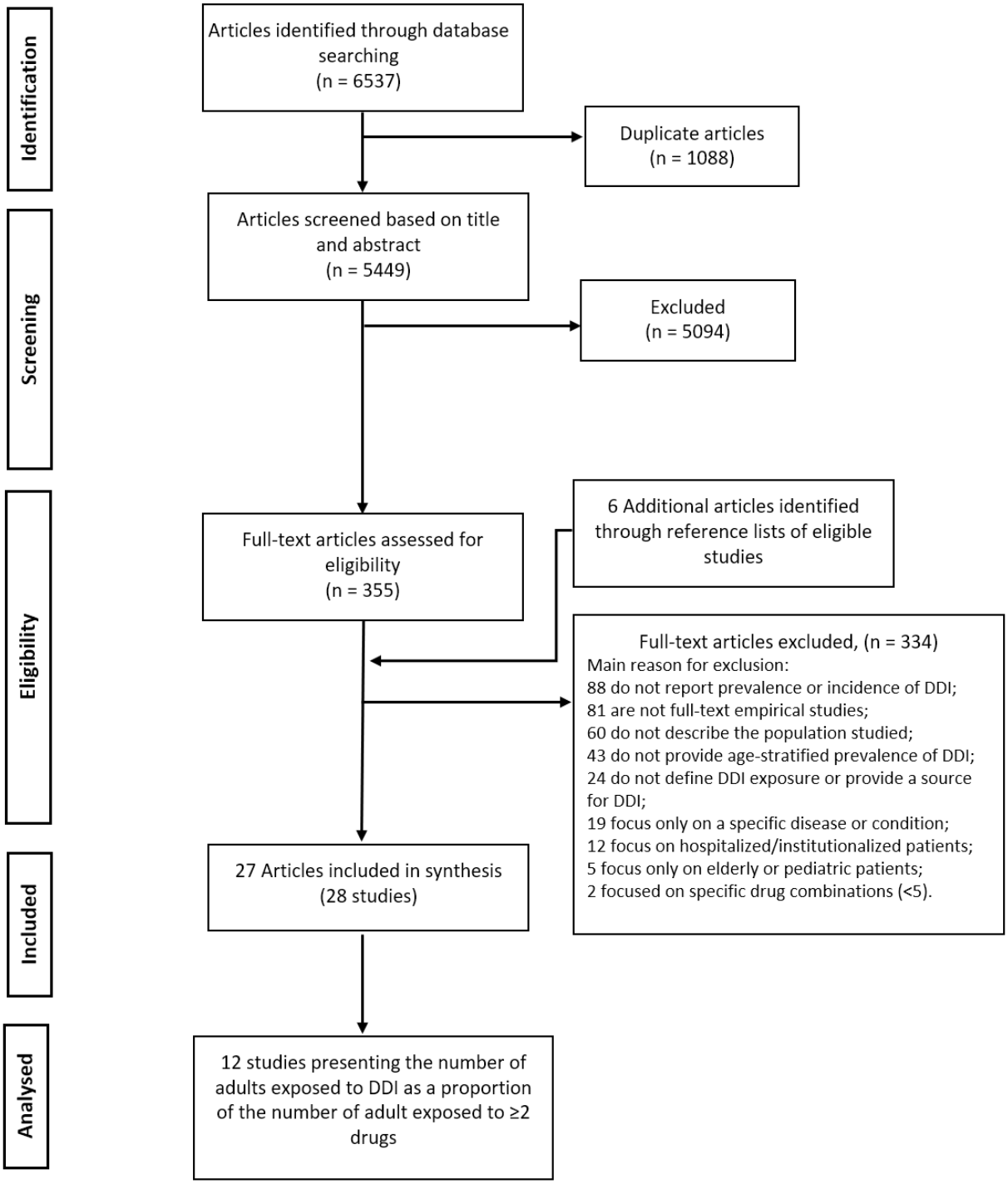

Figure 4-1. PRISMA flowchart of study selection

4.5.2 Study characteristics

All 28 included studies were published between 1978 and 2018. The length of the study period ranged from 2 to 84 months. Studies were conducted in Europe (11 studies reported in 10 publications)[15, 29-37], the United States (n=7)[38-44], Asia (n=6)[45-51], and Latin America and the Caribbean (n=3).[52-54] Characteristics of studies included in the meta-analyses are presented in Table 1; characteristics of all studies included in the narrative synthesis but excluded from the meta-analyses are presented in supplemental material Table S1.

Table 4-1. Characteristics of 12 studies included in the meta-analyses

Citation	Study year, duration	Setting	Population and age included	Reference for DDI identification and Type of DDI studied	DDI definition
Studies considering dispensed or claimed drugs to patients					
Astrand 2006, [29] Astrand 2007[30]	2003-04 15 months, cross-sectional	Population-wide in a small, mainly rural county Sweden (Jamtland cohort)	All people who purchased two or more prescription drugs at community pharmacies. Ages 15-64	Pharmaceutical Specialties in Sweden, 2003; Clinically significant only (studies 1 and 2) All DDI (study 3)	Dispensed prescriptions of two interacting drugs over fixed period (15 months)
Bjerrum 2003[31]	1999, 12 months, longitudinal	Population-wide in the county of Funen, Denmark	Individuals with at least one instance of temporally overlapping prescription drugs. Ages 20-59	Hansten and Horn 2002; All DDI, results stratified by DDI severity	Temporal overlap between two interacting drugs
Guthrie 2015[15]	2010, 12 weeks, cross-sectional	Population-wide in Tayside region, Scotland	All people aged 20 or older, resident in the region at least one year and registered with the National Health Service (NHS), who purchased two or more prescription drugs at community pharmacies. Ages 20-59	British National Formulary 59 (2010); Clinically significant DDI.	Dispensed prescriptions of two interacting drugs over fixed period (84 days)
Jazbar 2017[34]	2015, 12 months, longitudinal	Population-wide in Slovenia	All residents of the country who had at least two drugs dispensed, with at least one of them being a drug in a DDI of interest. Ages 20-64	Lexi-Interact 2017; Those involving one of 196 object drugs leading to clinically significant DDI (most frequently prescribed in Slovenia)	Interacting drugs dispensed to one patient on the same day

Citation	Study year, duration	Setting	Population and age included	Reference for DDI identification and Type of DDI studied	DDI definition
Maheshwari 2016[47]	No year stated, 6 months	Urban community pharmacies, India	Patients with prescriptions with three or more drugs, where a DDI was suspected by a physician. Ages 4-50	Micromedex; All DDI.	Concomitant claims
Siby 2016[49]	2015, 5 months	Healthcare setting: outpatients from two hospitals in Bangalore, India	Patients with prescriptions with two or more drugs. Ages 17-49	Micromedex; All DDI.	Concomitant claims
Tragni 2013[37]	2004-05, 20 months, longitudinal	Population-wide in two Italian regions	All residents who received at least one prescription of the selected drugs by a general practitioner or family paediatrician. Ages 0-64	Micromedex; 27 clinically significant DDI with excellent or good documentation, involving 144 highly prevalent drugs covered by the National Health Service (NHS)	Two definitions: prescriptions issued on the same day (co-prescription), and two drugs with temporally overlapping prescriptions (concomitant prescription)
Studies including prescriptions issued by a healthcare provider					
Beers 1990[38]	1988, two months	Healthcare setting: outpatients visiting an Emergency Department but not admitted to the hospital, USA	All subjects over 65 who visited the ED but were not admitted, and matched by date of ED visit, people under 60 for each person over 65 included. Ages 17-60	The Medical Letter for Drugs and Therapeutics; Clinically significant DDI.	Current use with DDI introduced at the ED

Citation	Study year, duration	Setting	Population and age included	Reference for DDI identification and Type of DDI studied	DDI definition
Chavda 2015*[50]	2013, six months	Healthcare setting: patients in the outpatient department of a tertiary care hospital	Patients visiting the outpatient department during the study period, who had at least one prescription. Ages 9-64	Drugs.com; All DDI.	Concomitant prescriptions
Linnarsson 1993[35]	1986-1990, 48 months	Healthcare setting: outpatients visiting a primary care clinic, Sweden	Patients who received two or more concurrent drugs. Ages 0-64	Swedish drug catalogue, with Hansten and Horn's classification; Clinically significant only (major) DDI	Temporal overlap between two interacting drugs
Patel 2014[48]	No year stated, five months	Healthcare setting: outpatients in a tertiary care teaching hospital, India	Patients of the Medicine Outpatient Department of a tertiary teaching care hospital, with two or more prescriptions and duration of use of 14 or more days. Ages 0-60.	Medscape; All DDI.	Concomitant prescriptions
Stanaszek 1978[41]	Year of study not stated, four months	Healthcare setting: outpatients visiting clinics in a government hospital, USA	All outpatients who received a new prescription containing at least two hospital formulary drugs from an outpatient clinic (same as whole pop). Ages 0-65.	Hansten and Horn; 97 Clinically significant DDI (moderate and major)	Current use by patient at the time of the study, based on new and refill prescriptions

4.5.3 Patient drug data used in the identification of DDI

Three sources of patient drug data were used in the included studies. First, patient health records that indicate prescriptions issued to patients by a prescriber (10 studies).[35, 36, 38, 39, 41, 46, 48, 50-52] Second, patient interviews to assess current drug use, including over-the-counter (OTC) drugs (three studies).[43, 52, 53] Third, data on drugs dispensed to patients at a pharmacy, usually from administrative claim databases (15 studies).[15, 29-34, 37, 40, 45, 47, 49, 51, 54]

4.5.4 Definition of DDI

Three main definitions of exposure to drugs which can potentially lead to DDI were presented in the included studies. A first definition was concurrent prescription or purchase of two or more drugs on the same day, on the same prescription sheet, or within a fixed time period (16 studies).[15, 29, 30, 33, 34, 37, 41, 45-51] This period of time ranged from one day to 15 months. A second definition was temporal overlap of two or more drugs. Six studies considered the expected duration of the prescription in order to identify periods of overlapping drugs; only drug pairs appearing within a temporal overlap were assessed for the presence of potential DDI.[31, 32, 35-37, 40] One study [37] reported the frequency of DDI using two different definitions: any temporal overlap, or drugs dispensed on the same day. In this study, a temporal overlap produced 52% higher prevalence of DDI than considering a prescription of two drugs dispensed on the same day (57,875 vs. 38,057 individuals exposed to at least one DDI during the study period). A third definition consisted in current use of two or more drugs. Five studies assessed for the presence of potential DDI within drugs currently used by patients on the day of data collection,[38, 39, 43, 52, 53] assessed by a combination of prescribed and dispensed drugs, and patient interviews.

4.5.5 Reference for the Identification of DDI

The most commonly used reference to classify a drug pair as potentially interacting was Micromedex, used in eight studies.[37, 39, 43, 46, 47, 49, 52, 53] Other references were used in two studies each: Hansten and Horn[31, 41], Malone et al.[32, 42], and Drugs.com.[45, 50] In addition, four national DDI compendia were used in six studies: *Swedish Drug Catalogue*,[35] *Pharmaceutical Specialties in Sweden 2003*,[29, 30] the *British National Formulary 59-2010*,[15] and the compendium of the General Council of the College of Pharmacists of Spain.[36] Three studies used multiple sources to classify drug pairs as potential DDI: one study used the *Swedish Drug Catalogue* and the DDI classification system proposed by Hansten and Horn,[35] another study combined three DDI reference sources (Hansten and Horn (1998) *Managing Clinically Important Drug Interactions*; Zucchero (1999) *Evaluations of Drug Interactions*; and Tatro (2000) *Drug Interaction Facts*),[51] and one used the Mediquick (Biostat) program to identify DDI, with the classification used by the French health protection agency, AFSSAPS.[33] Other sources used were the list of DDI published by *The Medical Letter for Drugs and Therapeutics*,[38] Lexi-Interact,[34] Cerner Multum©,[40] Medscape,[48] and Epocrates.[54]

4.5.6 Type of DDI

Studies assessing the frequency of DDI may choose to include all known DDI, or they may restrict their focus to only those DDI with the potential to lead to major or severe clinical adverse events (clinically significant DDI being also called clinically important or relevant). Out of the included 28 studies, 16 reported only the prevalence of DDI classified as clinically significant, 10 reported only the prevalence of all DDI (i.e., all predicted DDI at the time of publication, regardless of clinical severity and documentation), [29, 31, 45-54][22, 24, 38-47] while two reported both the prevalence of clinically significant DDI and of all known DDI.[29, 31]

4.5.7 Setting

Fourteen studies were whole-population studies.[15, 29-34, 36, 37, 40, 45, 47, 54] Of those, 13 relied on national or private administrative health databases recording all dispensed drugs (pharmaceutical claims data). One relied on an administrative health database of prescribed drugs. The health care settings of the 14 other studies were as follows: 1) Nationally-representative surveys of DDI prescribed in healthcare settings were used in three studies.[36] [42, 44] 2) In 11 studies, convenience samples of patients were recruited in healthcare settings such as outpatient clinics of hospitals,[41, 42, 46, 48-51] outpatients visiting the emergency department,[38, 39, 44, 52] primary health care clinics,[35, 36, 53] and community pharmacies.[45, 47]

4.5.8 Risk of bias within studies

Results of the appraisal are presented in the online supplemental material Table 4-8. Risk of bias scores ranged from 2.5 to 6.5 out of 7 (higher value means lower risk of bias). All studies were included in the meta-analysis regardless of their risk of bias score, with sensitivity analyses conducted for studies deemed at high risk of bias (score <3).

4.5.9 Results of individual studies

The results from the 12 studies included in meta analysis are detailed in Table 2; results of the studies included in the descriptive synthesis but excluded from the meta-analyses are presented in supplemental material Table S2. Among these, twelve studies reported the proportion of non-elderly adults exposed to at least one DDI among those exposed to two or more drugs and were included in the meta-analysis.

Table 4-2. Results of studies included in the meta-analyses: outcomes with explanations

Reference (study year)	Numerator with description	Denominator with description
Astrand 2006,[29] Astrand 2007[30] (2003-04)	981 individuals 15-64 years old exposed to at least one clinically significant (type C, D) DDI over 15 months.	5,028 individuals aged 15-64 with two or more drugs dispensed during the study period.
Beers 1990 (1988)[38]	10 individuals 17-60 years old with a DDI upon arrival at the ED..	52 individuals aged 17-60 arriving to the ED with two or more drugs.
Bjerrum 2003 (1999)[31]	554 individuals 20-59 years old exposed to at least one major DDI.	78,786 individuals aged 20-59 with at least one instance of temporally overlapping drugs.
Chavda 2015 (2013) [50]	124 individuals 9-64 years old exposed to at least one DDI	222 individuals aged 9-64 with two or more prescriptions.
Guthrie 2015 (2010) [15]	10,466 adults 20-59 years old exposed to "potentially serious" DDI	64,640 adults aged 20-59 exposed to two or more drugs.
Jazbar 2017 (2015) [34]	83,729 adults 20-64 years old exposed to at least one clinically significant DDI	652,753 adults aged 20-64 exposed to at least 2 drugs, with one drug being one of 196 object drugs.
Linnarsson (1986-90) 1993 [35]	138 individuals 0-64 years old exposed to at least one major DDI	3,488 individuals with at least two drugs, aged 0-64.
Maheshwari 2016 (no study year) [47]	45 people 4-50 years old with at least one DDI	101 people aged 4-50 years, who were dispensed three or more drugs, and for whom a DDI was suspected by a physician
Patel 2014 (no study year) [48]	171 patients aged less than 60 years received at least one DDI	217 patients less than 60 years in the study with two or more prescriptions and duration of use of at least 14 days

Siby 2016 (2015) [49]	51 people 17-49 years old with at least one DDI	213 people aged 17-49 prescribed two or more drugs
Stanaszek 1978 (no study year) [41]	572 individuals 0-65 years old exposed to at least one of 97 clinically significant DDI (moderate and major severity)	2,541 individuals aged 0-65 with two or more drugs within a new prescription containing at least two hospital formulary drugs from an outpatient clinic.
Tragni 2013 (2004-05) [37]	57,875 individuals 0-64 years old exposed to at least one of the 27 DDI within a temporally overlapping prescription.	632,026 people aged 0-64 exposed to at least one drug involved in 27 select DDI.

4.5.10 Results of the main synthesis

The pooled prevalence and rate of exposure to a DDI are presented in Figure 2. The pooled prevalence of exposure to DDI among adults exposed to two or more drugs was 0.18 (95% CI 0.09 – 0.35; PI 0.01 – 0.80); the pooled rate of exposure to at least one DDI of these same studies was 20.12 DDI per 1,000 person-months exposed to two or more drugs (95% CI 7.25 to 55.84 DDI per 1,000 person-months, PI 0.57 – 152.07). High heterogeneity was shown by τ^2 values being above 0.

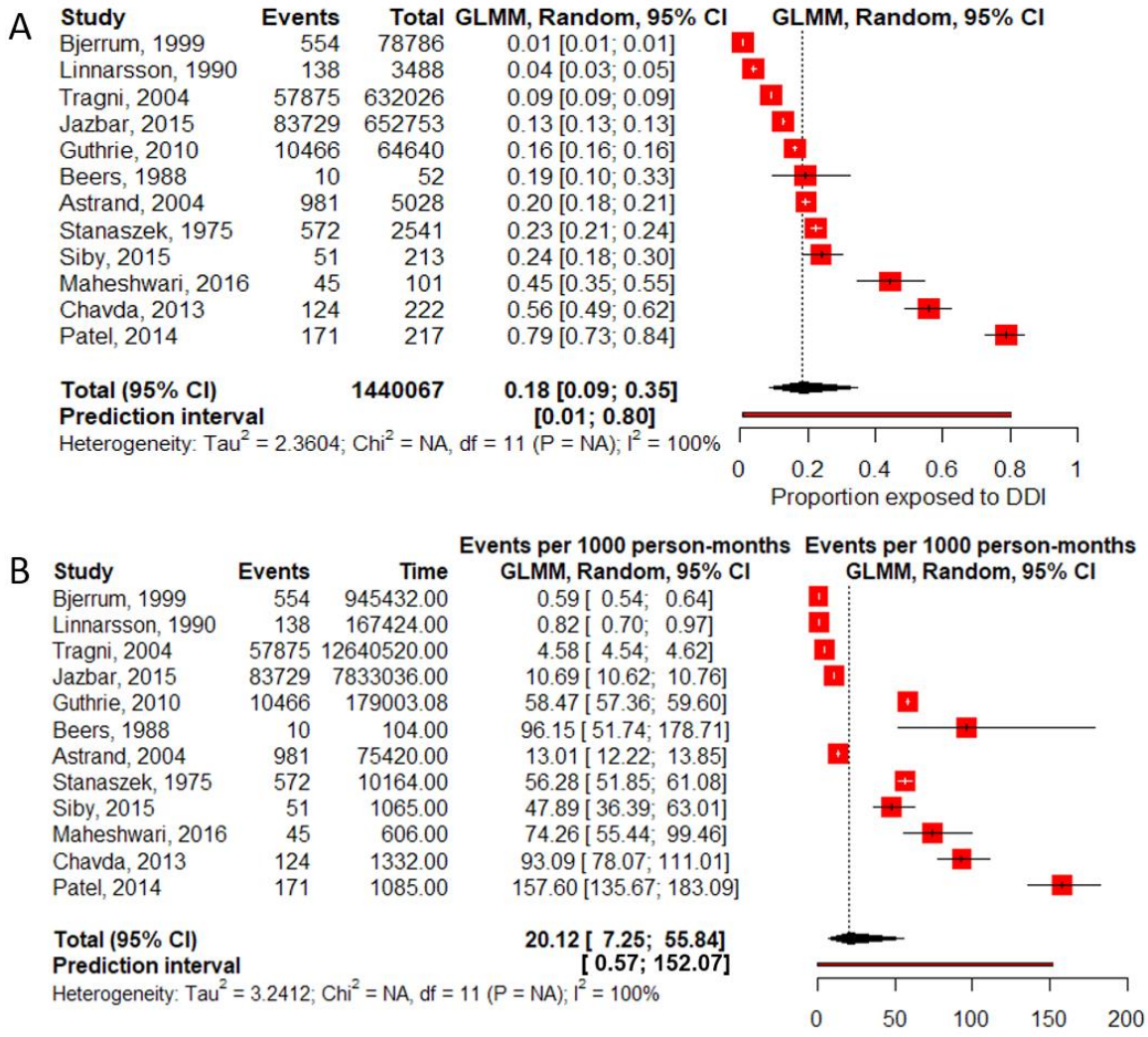

Figure 4-2. A. Forest plot of prevalence meta-analysis B. Forest plot of rate of DDI exposure per 1000 person months. Study years presented refer to the year of data collection.

4.5.11 Risk of bias across studies

High heterogeneity was observed (τ^2 of 2.36 and 3.24 for prevalence and rate respectively). Funnel plots presented in supplemental material Figure S1 show asymmetric distribution of prevalence and rate estimates.

4.5.12 Additional analyses

The small number of studies presenting comparable outcomes precluded us from conducting a meta-regression to assess the role of each study method on the estimates of DDI frequency. Subgroup analyses of the prevalence of DDI exposure revealed considerable heterogeneity within each subgroup (supplemental material Table S3). PI were narrower for studies considering only clinically important DDI (pooled prevalence estimate 0.13, 95% PI 0.04-0.35 vs. 0.28, 95% PI 0.01-0.82 for studies including all DDI), for studies assessing DDI within temporally overlapping drugs (pooled prevalence estimate 0.07, 95% PI 0.01-0.25 vs. 0.33, 95% PI 0.13-0.82 for studies not considering temporally overlapping drug exposures), and for studies using dispensed or claimed drugs as a source of data to assess DDI (pooled estimate 0.13, 95% PI 0.01-0.49 vs. 0.18, 95% PI 0.04-0.82) (Figure 3, supplemental materials Tables S3 and S4).

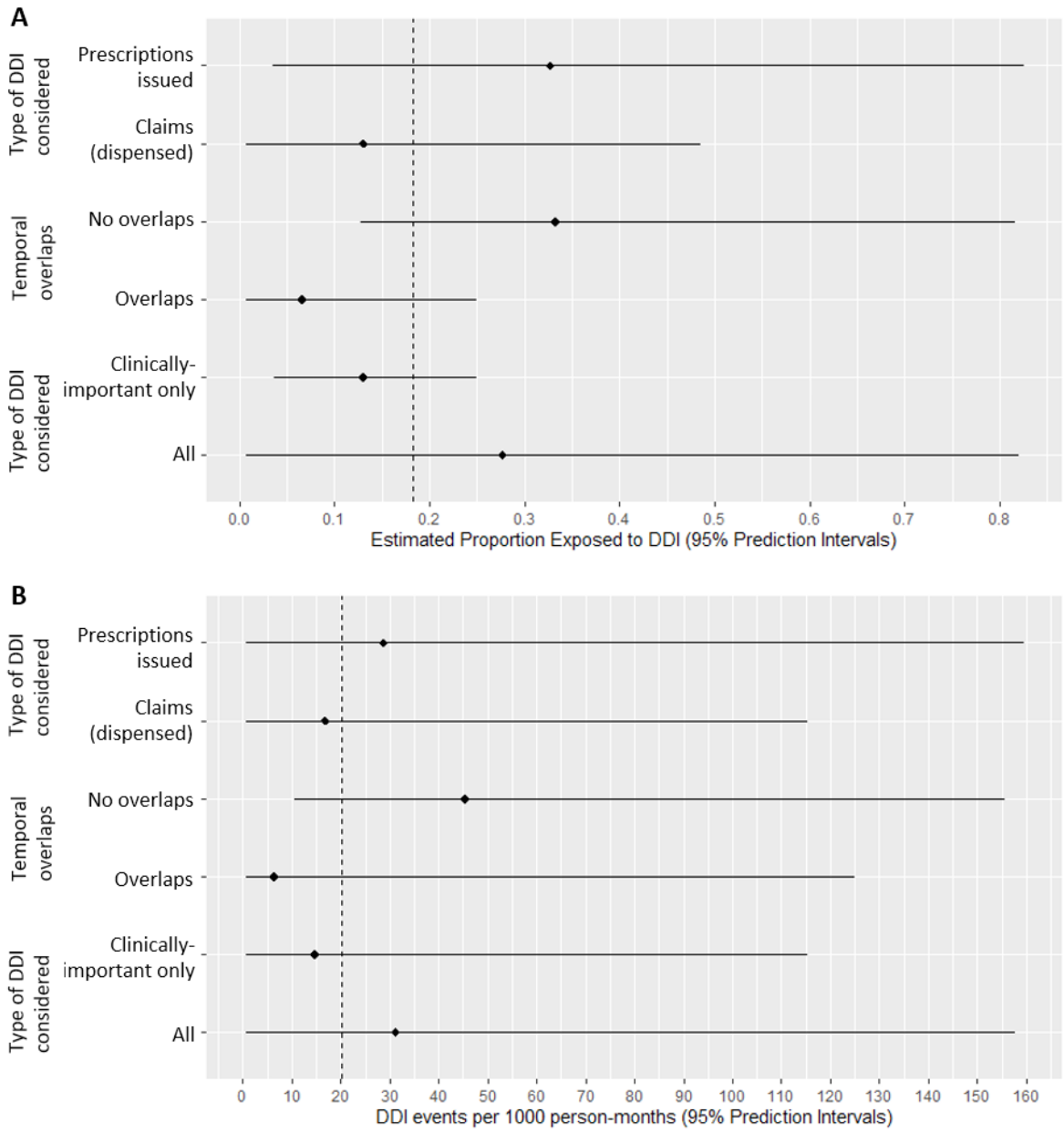

Figure 4-3. Prediction intervals by methodological characteristics.

Three variables were considered for this sub analysis: source of drug information (claims for dispensed drugs vs. prescriptions issued by healthcare provider), assessment of DDI only within temporally overlapping drugs (temporal overlap considered vs. not considered) and type of DDI considered (all predicted DDI vs. only DDI with a risk of producing a clinically important ADR. A. Pooled prevalence of exposure to DDI with 95% PI computed by parametric bootstrapping. B. Pooled estimates of the rate of DDI exposure with 95% PI computed by parametric bootstrapping

4.6 Discussion

Results of this review show that the prevalence of exposure to DDI among non-elderly adult outpatients exposed to two or more drugs varied widely in the included studies. The meta-analysis yielded a pooled prevalence estimate of 0.18 (95% CI 0.09-0.35, 95% PI 0.01 – 0.080, range 0.007 - 0.79). To account for varying study lengths, an analysis of the rate of exposure to DDI among non-elderly adult outpatients exposed to two or more drugs yielded a pooled rate of DDI of 20 events of DDI exposure per 1,000 person-months of follow up (95% CI 7.25 – 55.84. 95% PI 0.57 – 152.07, range 0.59 – 157.60). To our knowledge, this is the first systematic literature review with meta-analyses of the prevalence and the rate of exposure to DDI in a non-elderly adult population. The high heterogeneity of results suggests further research is needed on the prevalence and consequences of DDI in this population. In contrast, patients' exposure to DDI is better studied among elderly populations [9, 10] where DDI are estimated to account for 1.1 to 8.3 % of all hospital admissions. [11-13]

Systematic reviews of prevalence studies are useful to estimate the burden of a disease or of the exposure status, to help inform future research priorities and methods.[18] Our descriptive synthesis of 28 studies revealed a wide range of study methods used to assess the frequency of DDI in the population of non-elderly adult outpatients, including the sources of information used to assess drug exposure, the strategies used to assess the presence of two or more drugs, the drug interaction compendia used, and the types of DDI included.

The meta-analysis of 12 studies reporting the prevalence and event rate of adult exposure to at least one DDI among adults exposed to two or more drugs revealed high heterogeneity across the studies, which included 1,440,067 adults (Figure 2). Subgroup analyses conducted to assess the impact of pre-determined variables on heterogeneity estimates revealed high heterogeneity estimates in each subgroup, and wide PI.

The use of Freeman-Tukey double arcsine transformation for meta-analysing the prevalence estimates, as recommended,[26] resulted in misleadingly narrow PI likely due to the imbalance in sample sizes of included studies, as described by Schwarzer.[24] Using generalized linear mixed modeling corrected this in the case of the prevalence meta-analyses (see supplemental materials Figure S2) for a comparison of PI obtained from the different methods). However, using Poisson regression to pool rates of exposure to DDI led to an inflation of standard errors and associated PI widths. Thus, we used parametric bootstrapping to estimate the PI for event rates per 1,000 person-months of follow-up (see supplemental materials Figure S3 and Tables S3 and S4 for a comparison of the results obtained from the different methods).

Two main sources of heterogeneity were observed in this review: clinical and methodological.[27] First, there was an important clinical heterogeneity because studies selected different populations with differing baseline characteristics, e.g., all residents of a region in Scotland vs. patients seen at an emergency department in Taiwan. Second, the methods for assessing the presence of DDI varied widely, as did the source of patient information used to assess a DDI. The sub-analyses revealed that studies using pharmaceutical claims data had a tendency to report lower prevalence and lower rates of exposure to DDI, with narrower PI for the pooled estimates, compared to studies using prescription data that consider prescriptions issued by a healthcare provider but not necessarily purchased by the patients (usually from electronic medical records and chart reviews). Similarly, studies assessing the presence of DDI only within periods of exposure to two or more drugs (i.e., within temporally overlapping periods of drug exposure) showed lower pooled estimates and narrower PI, compared to studies that did not consider temporal overlaps. Interestingly, Tragni et al.[37] used two approaches to study DDI exposure in the same population and obtained different estimates of DDI prevalence: same-day dispensation (co-prescription) and temporally overlapped prescriptions. Conducting an analysis for

DDI among temporally overlapping drugs led to a considerable increase in the prevalence of DDI (temporally overlapped: 2.4 million DDI exposure events among 178,796 individuals vs co-prescription: 637,244 DDI events among 126,451 individuals).[37] This large difference in prevalence estimates obtained within a single population, using the same DDI reference data, in the same year, and with the same source of patient and prescription information underscores the importance of standardizing the choice of methods when conducting a study on the frequency of exposure to DDI.

4.6.1 Limitations and Strengths

This review faces some imitations. First, there was a lack of information regarding the number of potential DDI assessed in the included studies (i.e., how many DDI were included in the DDI compendia used in the study). Such information is crucial for understanding frequencies of exposure to DDI because the number of assessed DDI is likely associated with the observed frequency of exposure to DDI. Second, we were not able to statistically assess the impact of study methods on the observed frequency of exposure to DDI using meta-regression due to the low number of studies. Third, our calculation of person-time assumed that the duration of follow-up within studies was uniform, and that each exposed participant was exposed to a DDI only once per study period. Thus, the presented person-time estimates may be overestimated, artificially lowering the obtained rates. Fourth, there is a lack of consensus between lists used to identify DDIs (both in terms of interactions listed and their severity). Further research should focus on clinically significant DDI with high level of evidence. Lastly, no effort was made to compare the estimates we obtained to published studies measuring exposure to DDI among community-dwelling elderly adults (>64 years of age).

Regarding strengths, this review followed a systematic process where two independent reviewers were involved in the selection, quality appraisal and data extraction of studies. Moreover, two specialized librarians were involved in the development of the database search strategy. Regarding the meta-

analyses, we used a logistic regression with a logit transformation of the prevalence and a random intercept.[24] This solution was compared with meta-analysis of prevalence data using the Freeman-Tukey double arcsine transformation, and to parametric bootstrapping. Our analysis confirmed that the recommended Freeman-Tukey double arcsine transformation produced artificially narrow PI when pooling proportions of studies with a large range of sample sizes,[23] which we also observed in our analysis. To our knowledge, the present review is the first to confirm this issue. In addition, we uncovered an artifact leading to gross overestimation of PI of pooled rates using the recommended generalized linear mixed models and propose a universal bootstrapping method to compute PI in meta-analyses of proportions and rates.

4.6.2 Conclusions

Our results show that non-elderly adult outpatients' exposure to DDI is an important worldwide issue. In line with our results, future prevalence DDI research in this population should focus on clinically significant DDI, report the number of assessed DDI, use data on dispensed drugs, and consider temporal overlapped drug exposures.

4.7 Supplemental Material

Table 4-3. Characteristics of studies included in the descriptive synthesis but excluded from the meta-analyses.

Citation	Study year, duration	Setting	Population and age included	Reference for DDI* identification and Type of DDI studied	DDI definition
Studies considering drugs dispensed to or claimed by patients					
Astrand 2007[30]	3 studies: 1983-84, 1993-94, 2003-04 15 months each, cross-sectional	Population-wide in a small, mainly rural county Sweden (Jamtland cohort)	All people who purchased two or more prescription drugs at community pharmacies. Ages 15-64	Pharmaceutical Specialties in Sweden, 2003; Clinically significant only (studies 1 and 2) All DDI (study 3)	Dispensed prescriptions of two interacting drugs over fixed period (15 months)
Castro 2018*[54]	2017, three months	Population wide covering 13% of the country's population	Patients of any age with continuous prescriptions of 15 or more drugs (polypharmacy) between Jan 1 and March 31 2017. Ages 18-64	Epocrates; All DDI.	Temporal overlap between 2 interacting drugs
Gagne 2008[32]	2004, 12 months, longitudinal	Population-wide in one Italian region	All residents in the region. Ages 19-64	Malone et al 2004; 12 clinically significant DDI	Temporal overlap of ≥ 5 days between two interacting drugs
Guédon-Moreau 2004[33]	1999, three months, cross-sectional	Population-wide in two regions (called "departments") in the north of France	All people with at least one dispensed prescription over three months (residents in the two regions). Ages 20-59.	Mediquick DDI, validated by the French health protection agency AFSSAPS; Clinically significant only (contraindicated).	Dispensed prescriptions of two interacting drugs appearing on the same prescription sheet

Citation	Study year, duration	Setting	Population and age included	Reference for DDI* identification and Type of DDI studied	DDI definition
Kafeel 2014[45]	No year stated, no length	Small sample of population data (prescriptions from all pharmacies, clinics and hospitals), Pakistan	Patients in Karachi with two or more prescription drugs. Ages 16-49.	Drugs.com; All DDI.	Concomitant prescriptions
Ong 2017[40]	2008-11, 48 months, longitudinal	Population wide in the USA	All non-elderly adult beneficiaries enrolled in a commercial health plan, with two or more prescriptions issued by two or more different prescribers. Ages 19-64.	Cerner Multum; Clinically significant (major) DDI.	Overlap of more than 14 days, only if occurring more than once and through at least two different prescribers
Studies including prescriptions issued by a healthcare provider					
Gaddis 2002[39]	2001, 2.5 months	Healthcare setting: patients visiting the ED, USA	Convenience sample of 200 patients visiting the ED, including all outpatients 60 or older taking three or more drugs, and outpatients of any age taking five or more drugs. Ages 21-60.	Micromedex; Clinically significant (moderate or major severity) DDI, with good or excellent documentation	Current use with DDI introduced at the ED
Janchawee 2005[51]	2000, 12 months	Healthcare setting: outpatients visiting a hospital in Thailand	Outpatients who received at least one prescriptions during study period. Ages 20-59.	Own system compiled from Hansten & Horn 1998, Zucchero 1999, Tatro 2000; 1700 DDI.	Concomitant prescription (issued on same day, or within 1, 3, and 7 days)
Lin 2011[46]	2004, three months	Healthcare setting: outpatients of a medical centre, Taiwan	Outpatients with two or more prescriptions, with 14 or more days of duration of use. Ages 21-60.	Micromedex; All DDI.	Current prescriptions
Lopez 2010[36]	2007-08, two months separated by 15 months	Healthcare setting: outpatients covered by primary care clinics, Spain	All outpatients followed by participating family physicians. Ages 0-65.	General council of the College of the College of Pharmacists of Spain (BOT); 383 clinically significant DDI.	Temporal overlap between two interacting drugs

Citation	Study year, duration	Setting	Population and age included	Reference for DDI* identification and Type of DDI studied	DDI definition
Aparasu 2007[42]	2000-2002, duration unclear	Healthcare setting: national survey of in-person visits to ambulatory medical care clinics	Individuals accessing ambulatory medical care, selected using a multistage probability design. Ages 0-64.	Malone et al. 2004; 25 Clinically significant DDI	Concomitant prescriptions
Kim 2017[44]	2012, 84 months	Healthcare setting: nationally representative sample of ED visits	Adult patients going to the ED during study period, and whose patient record form included a prescription for an opioid, a benzodiazepine, or both. Ages 18-59.	Cerner Multum; Major (only benzodiazepine – opioid)	Concomitant prescriptions
Studies using patient interviews to assess drug exposure					
Dookeeram 2017[52]	No year stated, 4 months	Healthcare setting: outpatients in the ED of a tertiary care teaching hospital, Trinidad and Tobago	Convenience sample of patients visiting ED. All patients aged 18+ with triage score 2-5, presenting to ED but discharged after assessment and treatment. Ages 18-64.	Micromedex; All DDI.	Current use, including new prescriptions
Longo 2017[53]	2012-13, no length	Healthcare setting: patients at a basic health unit, Brazil	Patients with a medical appointment at a basic health unit. Ages 18-59.	Micromedex; All DDI.	Current use
Qato 2008[43]	2005-06,	Nationally representative probability sample	Community dwelling older adults. Ages 57-64.	Micromedex; Major DDI involving the 20 most common drugs and dietary supplements	Current use (regular use daily or weekly of two interacting drugs)

*DDI = drug-drug interactions

Table 4-4. Results of studies included in the descriptive synthesis: outcomes with explanations

Reference (study year)	Numerator with description	Denominator with description
Aparasu 2007 (2000-02) [42]	358 adult patient visits had at least one DDI prescribed	177,051total patient visits in the study 62,436 patient visits involved two or more drugs
Astrand 2007 (1983-84) [30]	896 individuals 15-64 years old exposed to at least one clinically significant (type C, D) DDI over 15 months	8318 individuals of all ages with two or more drugs dispensed during the study period
Astrand 2007 (1993-1994)[30]	973 individuals 15-64 years old exposed to at least one clinically significant (type C, D) DDI over 15 months	8,726 individuals of all ages with two or more drugs dispensed during the study period
Astrand 2006,[29] Astrand 2007[30] (2003-04)	981 individuals 15-64 years old exposed to at least one clinically significant (type C, D) DDI over 15 months. 2569 individuals 15-64 years old exposed to at least one DDI of all levels of clinical significance (A-D) over 15 months.	5,028 individuals aged 15-64 with two or more drugs dispensed during the study period. 8,214 individuals of all ages with two or more drugs dispensed during the study period (11,216 total population, all ages).
Beers 1990 (1988)[38]	10 individuals 17-60 years old with a DDI upon arrival at the ED. Five individuals 17-60 years old with a DDI introduced at the ED.	52 individuals aged 17-60 arriving to the ED with two or more drugs. 114 individuals aged 17-60 receiving new prescriptions for two or more drugs at the ED. 238 total population aged 17-60. 424 total population, all ages.
Bjerrum 2003 (1999)[31]	554 individuals 20-59 years old exposed to at least one major DDI. 4,062 individuals 20-59 years old exposed to at least one moderate DDI 1,594 individuals 20-59 years old exposed to at least one minor DDI 6210 individuals 20-59 years old exposed to at least one DDI of all levels of clinical significance over 15 months.	78,786 individuals aged 20-59 with at least one instance of temporally overlapping drugs. 161,612 individuals of all ages with at least one instance of temporally overlapping drugs. 471,732 total population, all ages.
Castro 2018 (2017) [54]	80 individuals 18-64 years old exposed to at least one DDI	80 individuals aged 18-64 with 15 or more prescription claims over three months.

		264 individuals of all ages with 15 or more prescription claims over three months.
Chavda 2015 (2013) [50]	124 individuals 9-64 years old exposed to at least one DDI	222 individuals aged 9-64 with two or more prescriptions. 253 individuals of all ages with two or more prescriptions. 300 individuals of all ages with at least one prescription.
Dookeeram 2017 (no study year) [52]	100 patients 18-64 years old were exposed to at least one DDI	374 adults aged 18-64. 544 patients of all ages with two or more prescriptions. 649 total adults included. All participants had a Canadian Triage Acuity Scale category 2-5 and were discharged from the ED after assessment and treatment.
Gaddis 2002 (2001) [39]	18 DDI of moderate or major severity, and with good to excellent documentation among individuals aged 21-60	74 adults presenting at the ED, aged 21-60. 200 total population included, aged 4-95.
Gagne 2008 (2004) [32]	1,268 adults 19-64 years old exposed to at least one of 12 clinically significant DDI for at least 5 days	4,222,165 total population residing in the region, all ages.
Guédon-Moreau 2004 (1999) [33]	3,035 adults 20-59 years old exposed to contraindicated DDI	1,754,372 people of all ages with at least one prescription for two or more drugs. 3,990,167 total population, all ages.
Guthrie 2015 (2010) [15]	10,466 adults 20-59 years old exposed to “potentially serious” DDI	64,640 adults aged 20-59 exposed to two or more drugs. 140,613 people of all ages exposed to two or more drugs. 183,726 people of all ages exposed to at least one drugs. 311,811 total population, all ages.
Janchawee 2004 (2000) [51]	41,111 prescriptions with a DDI	203,333 prescriptions issued to adults aged 20-59.

Jazbar 2017 (2015) [34]	83,729 adults 20-64 years old exposed to at least one clinically significant DDI	652,753 adults aged 20-64 exposed to at least 2 drugs, with one drug being one of 196 object drugs. 1,179,803 individuals of all ages exposed to two or more drugs. 2,063,077 total population, all ages.
Kafeel 2014 (no study year) [45]	202 prescriptions with DDI dispensed to people 16-49 years old	559 prescriptions dispensed to people aged 16-49
Kim 2017 (2012) [44]	623 patients 18-59 years old exposed to an opioid-benzodiazepine DDI	25,059 patients aged 18-59 who received at least one prescription for an opioid, a benzodiazepine, or both. 29,075 patients all ages who received at least one prescription for an opioid, a benzodiazepine, or both.
Lin 2011 (2004) [46]	10,525 adults 21-60 years old exposed to at least one DDI within overlapping prescriptions lasting 14 or more days	21,902 patients of all ages exposed to at least one DDI. 81,650 patients all ages visited the medical centre during study period.
Linnarsson (1986-90) 1993 [35]	138 individuals 0-64 years old exposed to at least one major DDI	3,488 individuals with at least two drugs, aged 0-64. 8729 individuals with at least one drug, aged 0-64. 6,008 individuals with at least two drugs, all ages. 12,651 individuals with at least one drug, all ages. 16,504 total population, all ages.
Longo 2017 (2012-13)[53]	62 people 18-59 years old with at least one DDI	118 people aged 18-59 prescribed two or more drugs in a basic health unit
Lopez 2010 (2007-08) [36]	905 adult patients exposed to at least one DDI pre-intervention (intervention designed to improve prescribing quality). 767 adult patients exposed to at least one DDI post-intervention	158,832 patients aged less than 65 years followed pre-intervention. 188,353 patients of all ages followed pre-intervention. 170,407 patients aged less than 65 years followed post-intervention. 202,983 patients of all ages followed post-intervention.
Maheshwari 2016 (no study year) [47]	45 people 4-50 years old with at least one DDI	101 people aged 4-50 years, who were dispensed three or more drugs, and for whom a DDI was suspected by a physician

Ong 2017 (2008-11) [40]	1,796 adults 19-64 years old exposed to a Major DDI within a temporal overlap of at least 14 days duration	88,494 individuals aged 19-64 enrolled in a commercial health plan
Patel 2014 (no study year) [48]	171 patients aged less than 60 years received at least one DDI	217 patients less than 60 years in the study with two or more prescriptions and duration of use of at least 14 days
Qato 2008 (2005-06) [43]	31 patients aged 57-64 years old exposed to at least one DDI	1,016 patients aged 57-64 included in the study. 2,976 patients aged 57-84 included in the study.
Siby 2016 (2015) [49]	51 people 17-49 years old with at least one DDI	213 people aged 17-49 prescribed two or more drugs
Stanaszek 1978 (no study year) [41]	572 individuals 0-65 years old exposed to at least one of 97 clinically significant DDI (moderate and major severity)	2541 individuals aged 0-65 with two or more drugs within a new prescription containing at least two hospital formulary drugs from an outpatient clinic. 3,028 individuals with two or more drugs, all ages. 3896 total population, all ages.
Tragni 2013 (2004-05) [37]	57,875 individuals 0-64 years old exposed to at least one of the 27 DDI within a temporally overlapping prescription. 38,057 individuals 0-64 years old exposed to at least one of the 27 DDI within a co-prescription.	632,026 people aged 0-64 exposed to at least one drug involved in 27 select DDI. 1,658,474 total population aged 0-64. 957,553 individuals exposed to at least one drug involved in 27 select DDI, all ages. 2,115,326 total population, all ages.

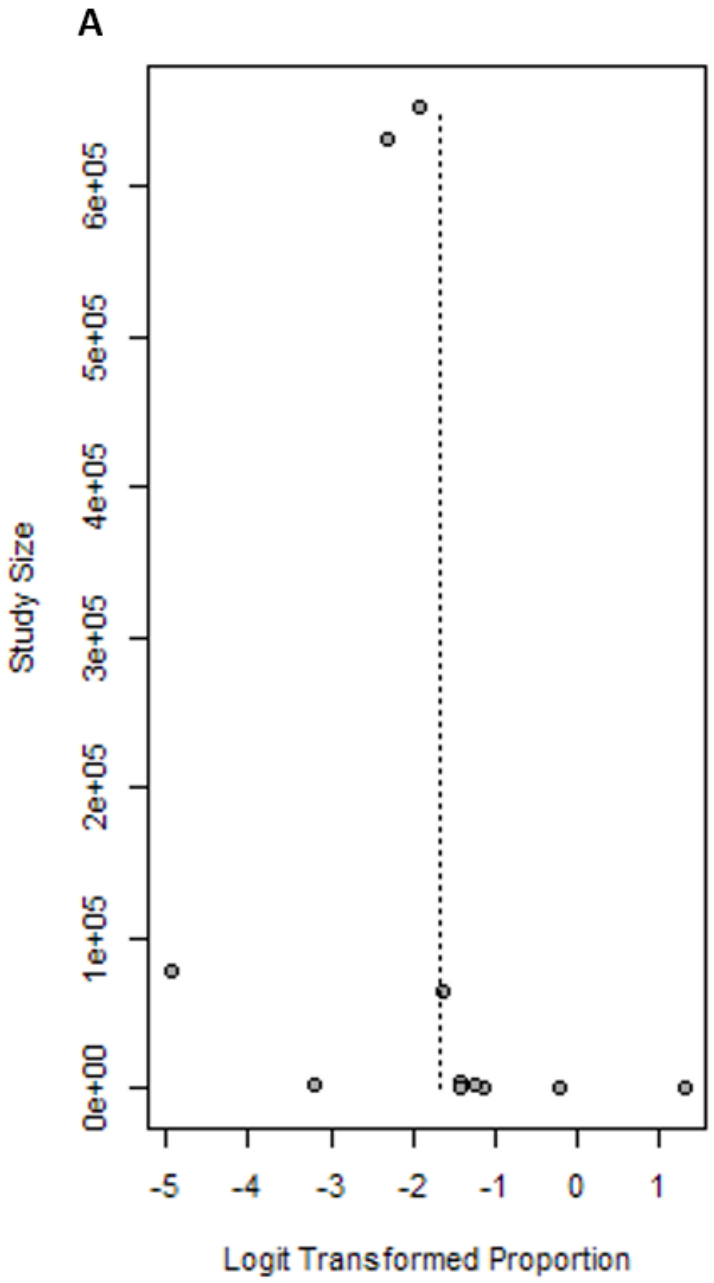

Figure 4-4. Funnel plot for prevalence of exposure to drug-drug interactions among individuals exposed to 2 or more drugs.

Table 4-5. Estimated prevalence and prediction intervals of exposure to DDI among studies included in meta-analysis.

Table presents the number of adults exposed to a DDI as a proportion of the number of adults exposed to two or more drugs or prescriptions. CI: confidence interval; GLMM: generalized linear mixed models with logit transformation; BS: parametric bootstrapping; PFT: inverse variance methods for pooling using Freeman-Tukey double arcsine transformed proportions used in conventional meta-analysis[26]

		N	Prevalence (95% CI)	95% Prediction interval			τ^2
				GLMM	BS	PFT	
	OVERALL	12	0.18 (0.09 – 0.35)	0.01 – 0.84	0.01 – 0.80	0.07 – 0.42	2.36
Source of data	Pharmaceutical Claims	8	0.13 (0.06 – 0.27)	0.01 – 0.69	0.01 – 0.49	0.03 – 0.35	1.66
	Prescriptions issued	4	0.33 (0.08 – 0.72)	0.01 – 0.95	0.04 – 0.82	0.00 – 1.00	2.85
Assessment of DDI	Overlap	5	0.07 (0.02 – 0.19)	0.00 – 0.56	0.01 – 0.25	0.00 – 0.56	1.81
	No overlap	7	0.33 (0.18 – 0.53)	0.05 – 0.83	0.13 – 0.82	0.19 – 0.45	1.17
DDI included	Major DDI	7	0.13 (0.09 – 0.19)	0.04 – 0.36	0.04 – 0.25	0.06 – 0.24	0.39
	All DDI	5	0.28 (0.05 – 0.72)	0.00 – 0.98	0.01 – 0.82	0.00 – 1.00	4.63

Table 4-6. Estimated rate and prediction intervals of exposure to DDI among studies included in meta-analysis

CI: confidence interval; GLMM: generalized linear mixed models with logit transformation; BS: parametric bootstrapping

		N	Rate of DDI per 1000 person months at risk (95% CI)	95% Prediction interval		τ^2
				GLMM	BS	
OVERALL		12	20.11 (7.25 – 55.84)	0.51 – 792.23	0.57 – 152.07	3.24
Source of data	Pharmaceutical Claims	8	16.81 (5.48 – 51.55)	0.59 – 479.55	0.56 – 115.38	2.60
	Prescriptions issued	4	28.65 (3.72– 220.39)	0.30 – 2737.71	0.73 – 159.45	4.33
Assessment of DDI	Overlap	5	6.39 (1.03 – 39.70)	0.07 – 555.16	0.56 – 125.0	4.32
	No overlap	7	45.46 (22.80 – 90.64)	6.51 – 317.48	10.60 – 155.76	0.86
DDI included	Major DDI	7	14.67 (4.66 – 46.15)	0.58 – 371.24	0.76 – 115.38	2.38
	All DDI	5	31.17 (5.26 – 184.65)	0.40 – 2420.91	0.56 – 157.60	4.11

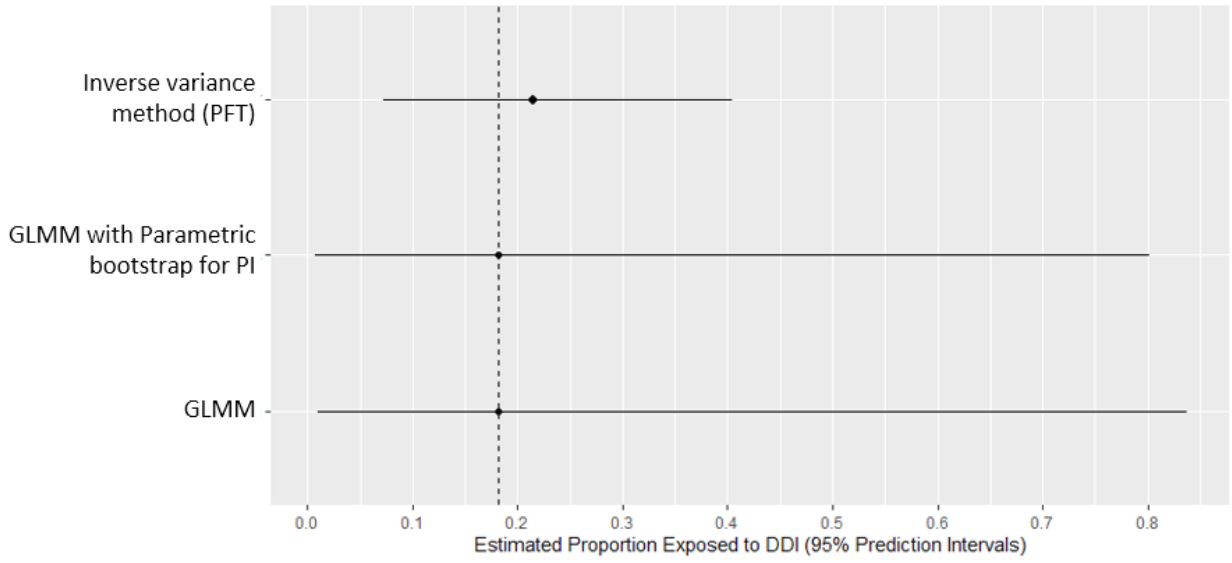

Figure 4-5. Comparison of results of pooled prevalence estimate and 95% prediction intervals by meta-analysis method.

Random effects meta analysis using inverse variance method with Freeman-Tukey double arcsine transformation produces artifactually narrow prediction intervals, as reported before,[24] which is corrected using both a random intercept logistic regression model (GLMM) with logit transformation of individual proportions, and parametric bootstrapping using a binomial distribution.

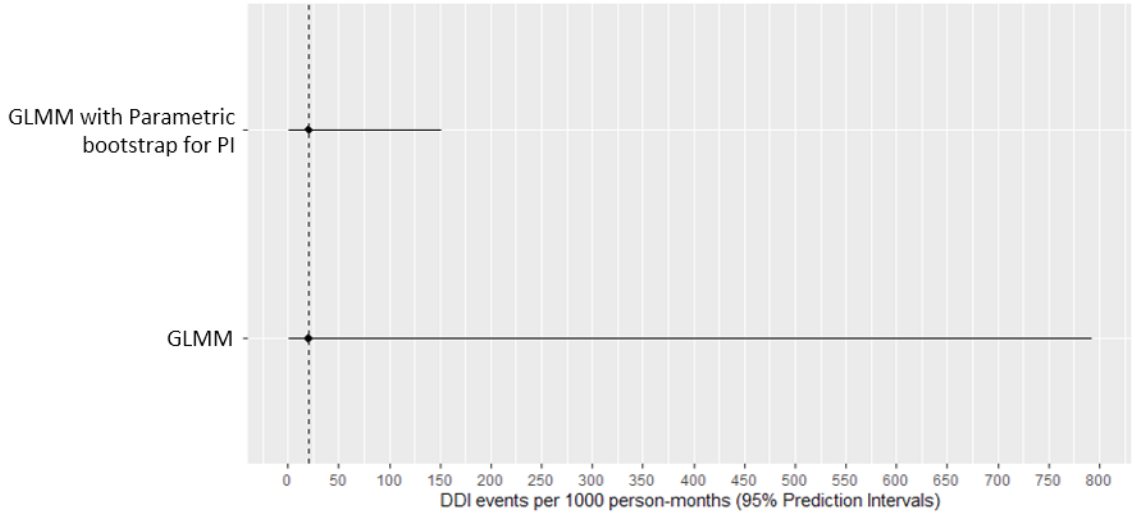

Figure 4-6. Comparison of 95% prediction intervals of pooled rates of exposure to a DDI by method of computation.

A random intercept logistic regression model (GLMM) with logit transformation of individual proportions using R package meta (metarate),[25] and parametric bootstrapping using a binomial distribution.

Search strategy in Medline

1 drug interactions/ or (($drug adj10 interact$) or "drug-drug").ti,ab. (118388)

2 ((drug$ or medication$ or medicine$ or medicament$ or treatment$ or prescription$ or pharmaceutical$) adj2 interaction$).mp. (114237)

3 1 or 2 (126488)

4 Prevalence/ or prevalence$.mp. or Incidence$.mp. or Incidence/ or retrospective studies/ or retrospective$.mp. or prospective studies/ or prospective$.mp. or Risk Factors/ or Cohort Studies/ or Cross-Sectional Studies/ or Health Surveys/ or Health Care Surveys/ or Mortality/ or cohort*.mp. or cross sectional.mp. or (health* adj2 survey*).mp. (3531838)

5 3 and 4 (12252)

6 (exp child/ or exp infant/ or adolescent/ or exp aged/) not (adult/ or middle aged/ or young adult/) (2489977)

7 elderly.m_titl. (103520)

8 (inpatient$ or "in-patient" or hospitali#ed or institutionali#ed or (nursing adj home)).m_titl. (59608)

9 cancer$.m_titl. or exp Neoplasms/ or oncol$.m_titl. (3399178)

10 exp HIV/ or HIV.m_titl. (239033)

11 Herbal Medicine/ or ((herbal adj medicine) or (herbal adj remedy) or herbal or homeopath$).m_titl. (13280)

12 (heart failure or hepatitis).mp. or (warfarin or kidney).m_titl. (583592)

13 intensive care.m_titl. (36184)

14 (schiz* or epilep* or (drug adj delivery) or (drug adj develop*)).m_titl,ab. (336081)

15 exp *Molecular structure/ (255630)

16 exp *Models, molecular/ (42679)

17 (dement* or diab* or tuber* or transplan* or senior* or (aged adj care) or (assisted adj living)).m_titl,ab. (1365469)

18 ((in adj vitro) or (in adj vivo) or (drug adj delivery) or (drug adj development)).mp. (2038341)

19 exp *"chemicals and drugs"/ (11993019)

20 exp clinical trial/ (873261)

21 or/6-20 (17481378)

22 5 not 21 (1560)

Table 4-7. Checklist used to appraise studies included in meta-analyses.

Adapted from Munn et al.[2]

Checklist items	Definition of response options for appraising included studies
Was the sample frame appropriate to address the target population?	The target population is defined, and the sample frame used is appropriate = 1; Target population defined but sampling frame inappropriate = 0.5; No target population specified = 0
Were study participants sampled in an appropriate way?	Randomized or full population = 1; Quasi-randomized = 0.5; Convenient sampling (e.g. only patients presenting to ER, clinic, or other setting) = 0
Were the study subjects described in detail?	3 things to look for: (1) Age (range and/or measure of central tendency); (2) Gender; (3) Number of drugs per person. Score as 1 if 3/3 are present, 0.5 if (1 or 2)/3 , 0 if 0/3
Was the setting described in detail?	3 things to look for: (1) Source of study data (Healthcare setting vs. national database); (2) Financing: public or privately funded; (3) Population served (urban, rural, rich, poor, etc). Score as 1 if 3/3 are present, 0.5 if (1 or 2)/3 , 0 if 0/3
Were valid methods used for the identification of the condition: Temporal Overlap	Explicit temporal overlap = 1; No overlap but less than 30 days between 2 Rx to be considered DDI = 0.5; No overlap, and there is more than 30 days separating Rxs that could interact
Were valid methods used for the identification of the condition: DDI detection	Computerized detection with a referenced source of DDI data = 1; non computerized, or source of DDI not clear = 0.5; Non computerized and source of DDI not clear = 0
Was there appropriate statistical analysis?	List of the measurements that will be made (frequency, prevalence, incidence, risk) with detailed analysis which is appropriate for the type of data and outcome = 1; List of the measurements with no analysis = 0.5; Inappropriate analysis or no details = 0

Table 4-8. Results of appraisal for 12 studies included in the meta-analysis.

	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Were the study subjects described in detail?	Was the setting described in detail?	Were valid methods used for the identification of the condition: Temporal Overlap	Were valid methods used for the identification of the condition: DDI detection	Was there appropriate statistical analysis?	**Total**
Astrand 2006[29]	1	1	1	1	0	1	1	**6**
Beers 1990[38]	1	1	1	1	1	1	0.5	**6.5**
Bjerrum 2003[31]	1	1	0.5	1	1	1	0.5	**6**
Chavda 2015[50]	1	0	1	0.5	1	1	1	**5.5**
Guthrie 2015[15]	1	1	1	1	0	1	1	**6**
Jazbar 2017[34]	1	1	1	1	1	0.5	1	**6.5**
Linnarsson 1993[35]	1	0	1	1	1	0.5	0	**4.5**
Maheshwari 2016[47]	0	0	0.5	0.5	1	0.5	0	**2.5**
Patel 2014[48]	0	0	1	0.5	1	0.5	1	**4**
Siby 2015[49]	0	0	1	0.5	1	0.5	0.5	**3.5**
Stanaszek 1978[41]	0	0	0.5	0.5	1	0.5	1	**3.5**
Tragni 2013[37]	1	1	1	0.5	1	1	1	**6.5**

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CHAPTER 5: Exposure to high-priority drug-drug interactions among non-elderly community dwelling adults in Quebec (Manuscript # 2)

5.1 Preface

The systematic review and meta-analysis (Manuscript 1, Objective 1) identified few studies measuring the prevalence of drug-drug interactions among non-elderly community-dwelling adults using administrative health data. Importantly, no studies conducted in Canada among this population were identified.

The present manuscript attempts to fill this knowledge gap by measuring the prevalence and incidence of exposure to drug-drug interactions among community-dwelling non-elderly adults in Quebec. Using provincial administrative health databases held by Quebec's National Institute for Excellence in Health and Social Services (INESSS), I conducted a longitudinal observational study measuring the one-year prevalence and incidence of exposure to high-priority drug-drug interactions. I describe the patterns of co-exposure among highly prevalent drugs using network analysis, and the results of predictive modelling using an ensemble machine learning approach.

I assessed whether the risk of exposure to drug-drug interactions over a one-year period can be predicted using the health service use and demographic data contained in these databases by measuring volume and continuity of care by clinician type (all physicians, family physicians, and pharmacists), multimorbidity, emergency department use, and hospitalizations. An accurate model could help in the prevention of exposure to high-priority drug-drug interactions.

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Exposure to high-priority drug-drug interactions among non-elderly community dwelling adults in Quebec

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5.2 Abstract

Background: Drug-drug interactions (DDI) constitute a recognized risk for certain patient populations. Their prevalence and incidence among the population of non-elderly community-dwelling adults in Quebec is unknown.

Objectives: (1) Estimate the one-year prevalence and incidence of exposure to high-priority DDI among community-dwelling non-elderly adults in Quebec covered by the public drug insurance; (2) describe the co-exposure patterns among the drugs involved in the most prevalent DDI; (3) identify the demographic and health system variables that predict risk of exposure to DDI.

Methods: We conducted a retrospective cohort study using provincial administrative health databases on 5% of community-dwelling adults aged 19-64 years covered by the public prescription drug insurance. Drug reimbursement claims were used to identify periods of overlapping exposure to ≥2 drugs between April 1, 2015 and March 31, 2016. DDI were identified using the list of high-priority DDI of the U.S. Office of the National Coordinator for health information. A network analysis was used to visualize the co-exposure to drugs involved in the most prevalent DDI. Demographic characteristics, health service use, continuity of care, and index of comorbidity were evaluated as predictors of exposure to DDI using an ensemble machine learning approach.

Results: Our cohort included 63,834 individuals aged 19-64 (mean age 44.9 SD 13.2, 51.6% female); among these, 34,131 (53.5%) claimed ≥2 drugs during the study year. The 12-month prevalence of exposure to DDI was 7,498/63,834 (11.7% of full cohort). Among 56,661 individuals at risk of incident DDI exposure, 2,695 (4.8%) were exposed to at least one DDI.

Number of drugs, continuity of prescriber and pharmacy care were identified as important predictors of exposure to DDI.

Conclusions: One in 8.5 non-elderly community-dwelling adults covered by the public drug insurance of Quebec is exposed to at least one high-priority DDI over 12 months. The clinical consequences of this exposure are unknown.

5.3 Introduction

Advances in pharmacotherapeutics have contributed to healthier populations with longer lifespans. In recent decades pharmacotherapy has shifted from short-term towards longer-term treatments to prevent and manage a variety of chronic conditions.[1] In this context, people's chronic exposure to multiple drugs concomitantly has increased.

Drug-drug interactions (DDI) arise when the effects of one drug cause changes in the behaviour of another drug, due to changes in active site concentration of one or both of the drugs and/or pharmacodynamic effects.[2] While DDI may be exploited for therapeutic purposes;[3] unintentional DDI may lead to adverse drug effects. DDI are expected to account for 20% of adverse drug reactions, and for 1.1–8.3% of hospital admissions.[4-6] Our systematic review on the prevalence of exposure to DDI among non-elderly outpatients found that exposure to a DDI varies widely between 0.7% and 78.8% of adults exposed to two or more drugs; this wide range in estimates likely reflects methodological and contextual differences between studies, and is consistent with findings from other systematic reviews measuring DDI exposure.[7, 8]

Exposure to DDI was found to be the probable or possible cause of 5.4% of hospitalizations over a one-month period.[9] Certain adverse effects arising from increased concentrations of a drug due to a DDI may be prevented through dose adjustments and monitoring of clinical precursors. Thus, the drug combinations to which each patient is exposed must be carefully monitored by primary care clinicians; continuity of care and carefully managed prescribing are essential to prevent known risks from exposure to a DDI.[10-12]

Canadian census data show that in the province of Quebec, 27.8% of the population older than 12 years did not have a regular healthcare provider in 2015. This proportion was higher among non-

elderly adults, with 45.2%, 30.4%, and 17.9% of adults aged 20 to 34, 35 to 44, and 45 to 64 years of age, respectively, compared with 9.6% of those aged 65 and over.[13] Those without regular access to a health care provider may have to rely on walk-in consultations and emergency department visits for their care. In addition to this fragmented primary care, the use of prescription drugs has increased in recent decades in Canada, with higher volumes of prescription drugs dispensed in Quebec compared to the rest of Canada.[14]

The extent to which non-elderly community-dwelling adults in Quebec are exposed to potentially harmful DDI is currently unknown; to our knowledge, no studies measuring the prevalence and incidence of exposure to DDI among the general non-elderly population have been conducted in Quebec or Canada.

5.4 Objectives

(1) To estimate the one-year prevalence and incidence proportion [15] of exposure to DDI among community-dwelling non-elderly adults in Quebec covered by the public drug insurance; (2) to identify the demographic and health system use variables which act as predictors of exposure to at least one DDI; (3) to describe the co-exposure patterns among the drugs involved in the most prevalent DDI (90^{th} percentile).

5.5 Methods

5.5.1 Study design and setting

We conducted a longitudinal cohort study using administrative health databases of the Canadian province of Quebec (estimated population in 2021: N=8,604,495).[16] Databases documenting pay-per-act medical consultations, hospitalizations and prescription drug claims of individuals covered by the public drug insurance between April 1, 2014 and March 31, 2016 were used. The study period went from April 1, 2015 to March 31, 2016, and the preceding year was considered the washout period during which exposure variables were measured (Figure S1 in the supplementary material).

5.5.2 Population

The source population [17] for this study consisted of all community-dwelling adults in Quebec (estimated population aged 18-64 years in 2015: 5,085,670,[18] of whom 1,386,760 were covered by the public drug insurance in 2015[19]). The database population comprised 1.2 million individuals aged 18 to 63 on April 1, 2014 with continuous coverage by the public drug insurance of Quebec between April 1, 2014 and March 31, 2017, regardless of their use of prescription drugs during this period. Individuals who resided in long-term care facilities at any point during the 3-year database period were excluded from the database population, as the focus of this study was exposure to DDI in the community. The study population was a 5% random sample without replacement of the database population; the sample size was selected based on the computational limitations of handling large numbers of prescription claims.

5.5.3 Variables

We extracted the following data for each participant: demographic information (9 variables), prescription medication claims (19 variables), medical services use (8 variables), and hospital admission data (10 variables). These were used to construct indicators for age, social and material deprivation index,[20] medication use during washout period, continuity of medical care by physician type[21] (overall, family physician), continuity of prescriber, continuity of pharmacy care (by pharmacy and by pharmacist),[22] number of hospitalizations, and multimorbidity (presence of 31 chronic conditions and a comorbidity index predictive of 30-day mortality[23]) (Table S2).

Assessment of drug exposure

Dispensed prescriptions were converted to a generic drug code developed using the algorithm in place at INESSS. Combination products were separated into their component drugs. Individuals were assumed to be exposed to the drug starting on the day of dispensation and for the duration specified in the claim. Oversupplies of each drug were carried forward; only drug doses expected to happen within the DDI assessment period were counted.[24] Drugs used during periods of hospitalization were not included, as these are not part of the RAMQ pharmaceutical claims database.

Assessment of exposure to high-priority DDI

Periods of overlapping drugs were identified for all individuals, and DDI were identified among temporally overlapping drugs.

A list of high-priority DDI was created, based on the list of the U.S. Office of the National Coordinator for Health Information Technology (ONC).[25] The ONC list includes QT drugs (those that are known to lead to drug-induced long QT syndrome). A list of all known and conditional QT drugs is maintained by the Arizona Centre for Education and Research on Therapeutics (AZCERT). The most recent version of the known and conditional QT drug list was downloaded on April 23, 2019. In addition, 84 DDI listed in the AZCERT website as "critical" were included, along with 252 potential DDI between benzodiazepine and opioid drugs.[26]

While the ONC list only specifies that any combination of the drug classes mentioned, and any two QT drugs should be avoided, it is not clear from existing evidence that combinations of any two QT drugs will lead to a DDI.[27] Thus, all QT drug pairs derived from the ONC list were assessed for the presence of potential pharmacokinetic/pharmacodynamic DDI using DrugBank.[28] The list of DDI from the ONC, with QT DDI pairs validated using DrugBank, contained 4,395 drug pairs expected to lead to high-priority DDI, and was used to identify exposure to a high-priority DDI during periods of overlapping drug treatments.

Individual patients were the unit of analysis for prevalent and incident DDI calculation. First, prevalent DDI cases were counted if an individual was exposed to at least one day of overlapping exposure to two drugs expected to lead to a DDI during the study period. An individual exposed to multiple different DDI was counted as a single case. Second, individuals were considered to have an incident DDI on the first day of exposure to a DDI during the study year if they were not exposed to any DDI during the covariate assessment period.

Covariates

All covariates are presented in Table S2 in the supplementary material. Demographic variables were age, sex, and an area-based index of social and material deprivation at the level of dissemination areas, assigned to individuals based on their address.[20] Continuity of care was measured using two validated methods: the Bice-Boxerman Continuity of care index (COCI)[29] and the Usual Provider of Care index (UPC).[30] As medical billing data may reflect multiple acts billed within one visit, one medical visit was defined as one encounter for each patient-physician combination per day. Six dimensions of continuity of care were assessed: (1) overall continuity considered all visits to physicians; (2) primary care continuity considered only visits to family physicians; (3) prescriber continuity considered the number of different prescribers associated with each patient's drug claims, (4) family physician prescriber continuity considered the number of different family physician prescribers associated with each patient's drug claims, (5) pharmacy continuity considered the different pharmacy establishments used to purchase drugs, and (6) pharmacist continuity, which considered the number of dispensing pharmacists. Both COCI and UPC of these six continuity-of-care dimensions were computed.

The number of outpatient visits was measured by considering all medical acts billed during the study period, and dispensed outside of dental, physiatrist, and optometrist practices. Medical acts occurring within hospital-based clinics were counted if they occurred outside of a period of hospitalization.

We used a validated algorithm to identify the presence of 31 chronic conditions and compute an index of comorbidity predictive of 30-day mortality using Quebec administrative health databases, the combined Charlson and Elixhauser index of comorbidity.[23]

5.5.4 Data sources

The Quebec public health insurer (RAMQ) and the Ministry of Health and Social Services administer public health and drug insurance plans in the province, and related databases. Four databases were used, linked using an anonymous identifier. First, the medical billing database contains data on all medical acts billed on a fee-for-service basis, the dominant form of physician remuneration in Quebec, including those in community clinics, private clinics, and hospitals; it includes a main diagnostic code for each act. The pharmaceutical claims database contains data on all prescriptions dispensed and covered under the public prescription drug plan, with the date of dispensation, the expected treatment duration, quantity, dose, and form of the dispensed drug. The dispensing pharmacist, prescribing physician, and pharmacy are indicated in each claim. The hospitalizations database holds data on all hospitalisations in the province and includes up to 25 diagnostic codes per hospitalisation. Visits to the emergency department are also recorded. The demographic file contains the date of birth, territory of residence, and the Quebec index of material and social deprivation.

5.5.5 Quantitative variables

Count and continuous variables were centred and standardized before being included as covariates predicting risk of exposure to a DDI. The UPC is only defined for individuals with at least one medical visit, while the COCI is only defined for those with at least two medical visits; thus, these indexes were modeled as categorical variables, with one category representing all undefined cases. All categorical variables were modeled as binary dummy variables.

5.5.6 Analytical methods

5.5.6.1 Predicting exposure to DDI

We used an ensemble machine learning approach to predict exposure to DDI. The R package SuperLearner [31] with ten-fold cross-validation was used to combine the predictions of six machine learning algorithms to predict exposure to at least one DDI during the study period.[32]: The SuperLearner [31, 33] is a method which finds the optimal (weighted) combination of a pre-specified collection of predictive models, leveraging the strengths of each one and improving classification accuracy when compared to applying a single predictive model. The included algorithms were: (1) a least absolute shrinkage and selection operator (LASSO);[34] (2) a recursive partitioning decision tree;[35] (3) random forest;[36] (4) fast-implementation random forest;[37] and, (5) extreme gradient boosting machine;[38]. The default hyperparameter settings in the algorithms were kept.

The data was divided into a training set containing a random sample of 75% of all observations (N=47,876 individuals), and the remaining 25% (15,958) were used to assess the model performance. The method of maximizing the area under the receiver-operator characteristics (ROC) curve (AUC) was used to fit a prediction model for exposure to at least one day of DDI during the study period (loss function 1-AUC).[39]

Variable importance measures were obtained using non-parametric ROC curve analysis for each predictor using the 'caret' package in R (version 6.0-86).[40] All variables were included in the models.

5.5.6.2 Drug co-exposure patterns

A network analysis approach based on frequent itemset mining methods, [41] was used to study and visualize the drug combinations involved in the most prevalent DDI (top 10^{th} percentile) based on the number of people exposed. The frequency of each drug combination was calculated as the number of exposed days per person.

The spectrosome shows co-exposure to the drugs involved in the most prevalent DDI. Each drug is represented by a node, each connected to the drug(s) found in co-exposure with it; colors indicate co-exposures predicted to lead to a DDI, and size indicates the proportion of person-days with drug overlap. The co-exposure tree shows the variety of DDI beyond pair-wise combinations. The heatmap shows the relative frequency of the drugs and their combinations according to the number of drugs involved.

5.6 Results

5.6.1 Participants

A total of 63,834 individuals with their corresponding 6.40 million drug claims, 1.80 million medical acts, 280,000 ER visits and 24,000 hospitalization episodes were included. Among them, 34,131 individuals (53.5% of study population) were exposed to two or more drugs during the study period; of these, 33,273 were exposed to at least one day of overlapping drugs, and 7,498 (11.7%, 95% CI: 11.5% to 12.0%) people were exposed to at least one DDI for at least one day during the study period (Figure 1). There were 56,661 individuals at risk of exposure to an incident DDI during the study period (no exposure to any DDI during the covariate assessment period), and 2,695 incident DDI cases occurred during the study year among them.

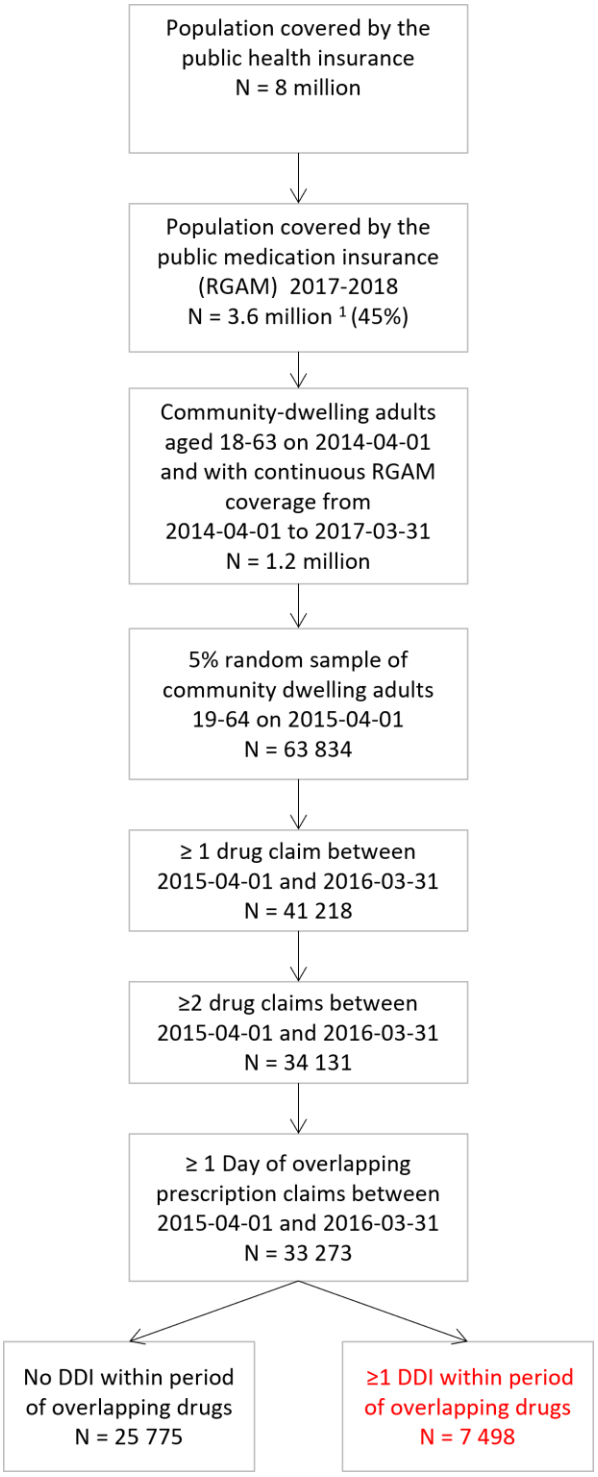

Figure 5-1. Participant flowchart – prevalent DDI

5.6.2 Descriptive data

5.6.2.1 Prevalent DDI

On average, those exposed to at least one prevalent DDI had a higher age (50.4 [SD 11.6, IQR 44-60] vs. 44.2 [SD 13.3, IQR 33-56] years), were more likely to be female (4,760/7,498 or 63.5%), had lower continuity of care (all six types, see Table 1), had higher multimorbidity index (0.31 [95% CI 0.29-0.34] vs. 0.10 [0.09-0.10]), and consumed more drugs than those unexposed to DDI (9.26 [9.13-9.40] vs. 2.54 [2.51-2.56] different drugs) (Table 1).

Table 5-1. Participant characteristics

Characteristic	No DDI (N = 56336, 88.3%)	≥ 1 DDI (N = 7498, 11.7%)	Total (N = 63834)
Sex at birth (N [%])			
Male	28185 (50.0%)	2738 (36.5%)	30923 (48.4%)
Female	28151 (50.0%)	4760 (63.5%)	32911 (51.6%)
Age (mean [SD])	44.2 (13.3)	50.4 (11.6)	44.9 (13.2)
Quintile of deprivation:			
1 (Least deprived)	7241 (12.9%)	702 (9.4%)	7943 (12.4%)
2	9279 (16.5%)	1084 (14.5%)	10363 (16.2%)
3	10976 (19.5%)	1329 (17.7%)	12305 (19.3%)
4	13377 (23.7%)	1905 (25.4%)	15282 (23.9%)
5 (Most deprived)	14867 (26.4%)	2385 (31.8%)	17252 (27.0%)
Missing	596 (1.1)	93 (1.2%)	689 (1.1%)
N Drugs (mean [SD])	2.5 (3.3)	9.3 (6.0)	3.3 (4.3)
Comorbidity Index (mean [SD])	0.10 (0.58)	0.32 (1.09)	0.12 (0.66)
Number of chronic conditions (mean [SD])	0.12 (0.38)	0.43 (0.71)	0.16 (0.44)
Affiliated with Family Physician (N [%])	34791 (61.8%)	6313 (84.2%)	41104 (64.4%)
Not affiliated with Family Physician (N [%])	21545 (38.2%)	1185 (15.8%)	22730 (35.6%)
MD Consulted, all specialties (mean [SD])	2.13 (2.79)	4.76 (4.79)	2.44 (3.20)
Bice-Boxerman COCI – all MD	0.42 (0.43)	0.32 (0.35)	0.41 (0.42)
Usual provider of care – all MD	0.62 (0.30)	0.52 (0.28)	0.61 (0.30)
FP consulted (mean [SD])	1.07 (1.42)	2.04 (2.22)	1.18 (1.57)
Bice-Boxerman COCI – FP only	0.63 (0.44)	0.55 (0.42)	0.62 (0.44)
Usual provider of care – FP only	0.78 (0.27)	0.72 (0.28)	0.77 (0.27)
Prescribers, all MD (mean [SD])	1.21 (1.47)	3.09 (2.32)	1.43 (1.71)
Bice-Boxerman COCI – all MD prescribers	0.64 (0.37)	0.54 (0.32)	0.62 (0.37)
Usual provider of care – all MD prescribers	0.77 (0.25)	0.68 (0.24)	0.76 (0.25)
Family physician PrescribersFP (mean [SD])	0.90 (1.13)	2.11 (1.65)	1.04 (1.26)
Bice-Boxerman COCI – FP prescribers	0.73 (0.36)	0.66 (0.33)	0.71 (0.35)

Characteristic	No DDI (N = 56336, 88.3%)	≥ 1 DDI (N = 7498, 11.7%)	Total (N = 63834)
Usual provider of care – FP prescribers	0.83 (0.23)	0.78 (0.23)	0.82 (0.23)
Pharmacists	2.47 (2.87)	6.12 (3.46)	2.90 (3.17)
Bice-Boxerman COCI – pharmacist	0.32 (0.34)	0.20 (0.17)	0.30 (0.32)
Usual provider of care – pharmacist	0.47 (0.29)	0.30 (0.17)	0.44 (0.28)
Pharmacies	0.86 (0.94)	1.59 (1.06)	0.95 (0.99)
Bice-Boxerman COCI – pharmacy	0.81 (0.31)	0.80 (0.28)	0.81 (0.30)
Usual provider of care – pharmacy	0.88 (0.21)	0.85 (0.21)	0.87 (0.21)
Outpatient Medical visits, all specialties	3.25 (5.87)	8.68 (12.36)	3.89 (7.17)
Outpatient medical visits, FP only	1.63 (2.49)	3.71 (4.09)	1.87 (2.81)
ER Visits	0.38 (1.09)	1.05 (1.05)	0.46 (1.32)
Days hospitalized	0.57 (5.68)	2.56 (12.96)	0.80 (6.97)

5.6.2.2 Incident DDI

The average age among those at risk for an incident DDI was 44.2 years (SD 13.3). Compared to individuals without an incident DDI, those individuals exposed to an incident DDI during the study period were older (48.1 [SD 12.7] vs. 44.0 [SD 13.3] years), more likely to be female (1,708/2,695 or 63.4%), had lower continuity of care (all six types), had higher multimorbidity index (0.20 [0.17-0.24] vs. 0.08 [0.08-0.09]), and consumed more drugs than those unexposed to DDI (5.75 [5.60-5.91] vs. 2.27 [2.25-2.30] different drugs).

5.6.2.3 Exposure to prescription drugs by community-dwelling adults in Quebec

We identified 673 unique drugs to which at least one individual was exposed during the study period; of these, 164 (24%) drugs were involved in at least one high-priority DDI during the study period. Nearly three-quarters of all prescriptions claimed to the public drug insurance of Quebec

(4,906,219/6,724,888 or 73%) were issued by a family physician, with all physicians combined accounting for the remaining prescription claims.

5.6.3 Primary Outcome: risk of exposure to at least one day of DDI over 12 months

5.6.3.1 Prevalent DDI

A total of 7,498/63,834 individuals (11.7% [95% CI: 11.5% – 12.0%] of the total population studied, 19.1% [18.7% – 19.5%] of those with two or more drug claims, and 22.5% [22.1% – 23.0%] of those with at least one day of overlapping drug exposure) were exposed to 850 high-priority DDI during the study period (Figure 1). This represented 30,385 episodes of DDI exposure, each one lasting a median of 15 days (mode 30, IQR 6-56, range 1-366 days). Durations of exposure to the ten most prevalent DDI are presented in Figure S2 in the supplementary material. DDI involving two drugs with known or conditional risk of leading to long QT syndrome account for 760/850 (89.4%) of these. The antipsychotic quetiapine was the most common drug among top prevalent DDI, appearing in 14 of the 50 most prevalent DDI (Table S1 in the supplementary material).

5.6.3.2 Incident DDI

A total of 2,695/56,661 individuals (4.8% [95% CI: 4.6% – 4.9%] of the population without exposure to a DDI during the baseline assessment period were exposed to one or more DDI during the 12-month study period, for a median duration of 7 days (mode 10, IQR 3-14, range 1-359) per exposure episode.

5.6.4 Prediction of exposure to a DDI

The ensemble SuperLearner model on the full population predicted exposure to prevalent DDI with an AUC of 0.90 on the test data, while exposure to incident DDI was predicted with an AUC of 0.78 (Table S3). The importance of each variable in predicting exposure to a DDI over one year is presented in Figure 4. The most important variables related to medication use (number of drugs claimed in the year preceding the study period), continuity of care (number of different pharmacists, number of different prescribers [all MD], number of different prescribers [FP only], more than one pharmacist seen, number of physicians seen [all MD], and no visits with an FP), and exposure to at least one DDI during the covariate assessment period (Figure 2).

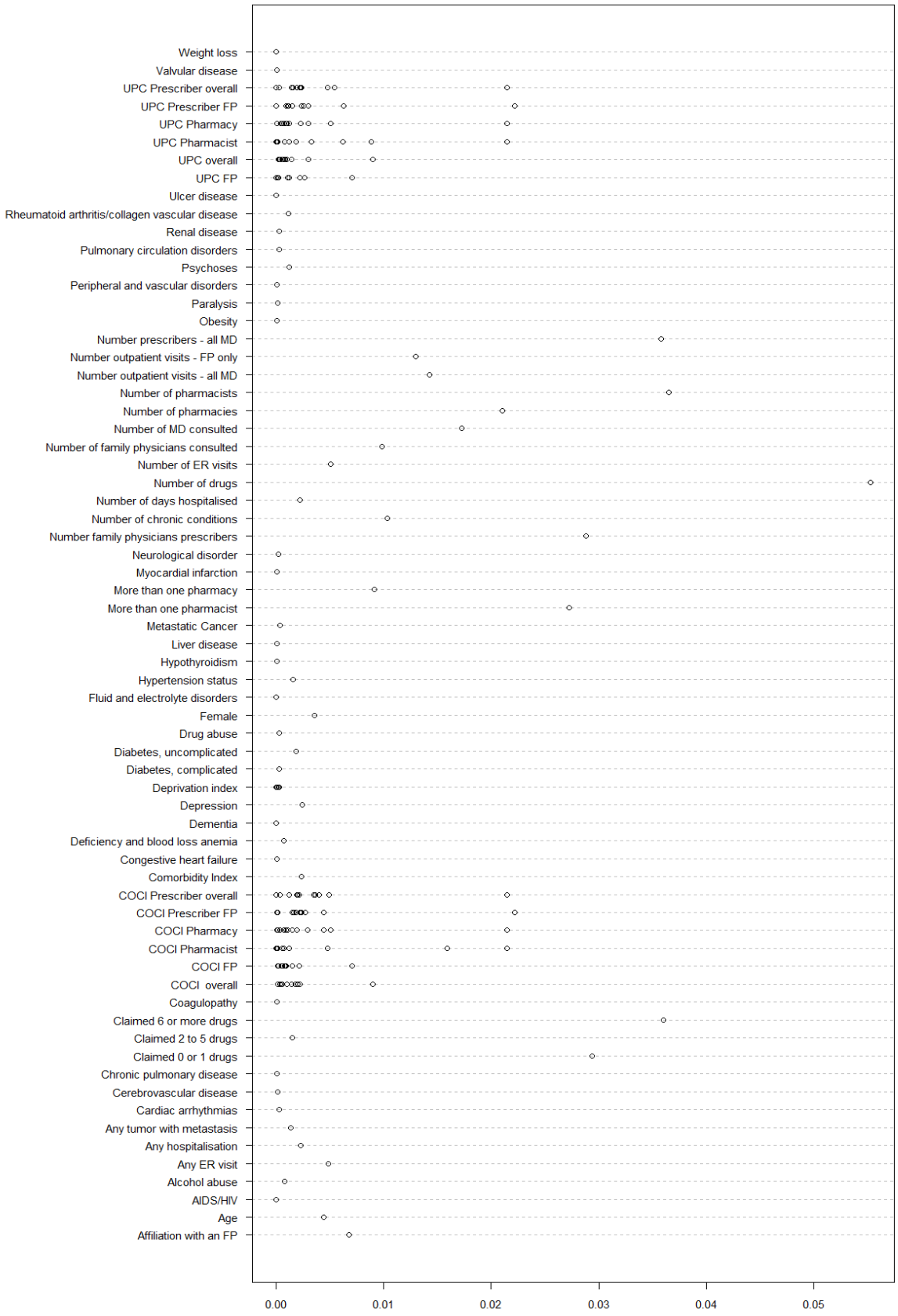
Weight loss
Valvular disease
UPC Prescriber overall
UPC Prescriber FP
UPC Pharmacy
UPC Pharmacist
UPC overall
UPC FP
Ulcer disease
Rheumatoid arthritis/collagen vascular disease
Renal disease
Pulmonary circulation disorders
Psychoses
Peripheral and vascular disorders
Paralysis
Obesity
Number prescribers - all MD
Number outpatient visits - FP only
Number outpatient visits - all MD
Number of pharmacists
Number of pharmacies
Number of MD consulted
Number of family physicians consulted
Number of ER visits
Number of drugs
Number of days hospitalised
Number of chronic conditions
Number family physicians prescribers
Neurological disorder
Myocardial infarction
More than one pharmacy
More than one pharmacist
Metastatic Cancer
Liver disease
Hypothyroidism
Hypertension status
Fluid and electrolyte disorders
Female
Drug abuse
Diabetes, uncomplicated
Diabetes, complicated
Deprivation index
Depression
Dementia
Deficiency and blood loss anemia
Congestive heart failure
Comorbidity Index
COCI Prescriber overall
COCI Prescriber FP
COCI Pharmacy
COCI Pharmacist
COCI FP
COCI overall
Coagulopathy
Claimed 6 or more drugs
Claimed 2 to 5 drugs
Claimed 0 or 1 drugs
Chronic pulmonary disease
Cerebrovascular disease
Cardiac arrhythmias
Any tumor with metastasis
Any hospitalisation
Any ER visit
Alcohol abuse
AIDS/HIV
Age
Affiliation with an FP
0.00
0.01
0.02
0.03
0.04
0.05

Figure 5-2. Variable importance at predicting risk of exposure to an incident DDI over 12 months among community-dwelling non-elderly adults covered by the public drug insurance. The X-axis represents the area under the receiver-operator curve for each individual predictor, which is used as the measure of variable importance.[40]

5.6.5 Drug co-exposure patterns

The 32 drugs involved in the most prevalent DDI (75th percentile) represented a total of 6,486,955 person-days of exposure. The most prescribed were hydrochlorothiazide (976,711 person-days), quetiapine (744,964 person-days) and citalopram (683,346 person-days) (Figure 3). Among the 32 drugs, 25 were found with at least one other drug on the same day at least 50% of the time, ranging from 29.8% for hydrochlorothiazide (290,730/976,711 person-days) to 73.2% of the time for morphine (38,771/52,938 person-days). Five other drugs were found in combination with other drugs in at least 70% of person-days of exposure during the study year: temazepam (71,454/98,676 person-days, 72.4%), hydromorphone (101,119/143,384 person-days, 70.5%), oxycodone (68,596/97,437 person-days, 70.4%), loperamide (15,853/22,558 person-days, 70.3%) and domperidone (74,585/106,479 person-days, 70%) (Figure 3).

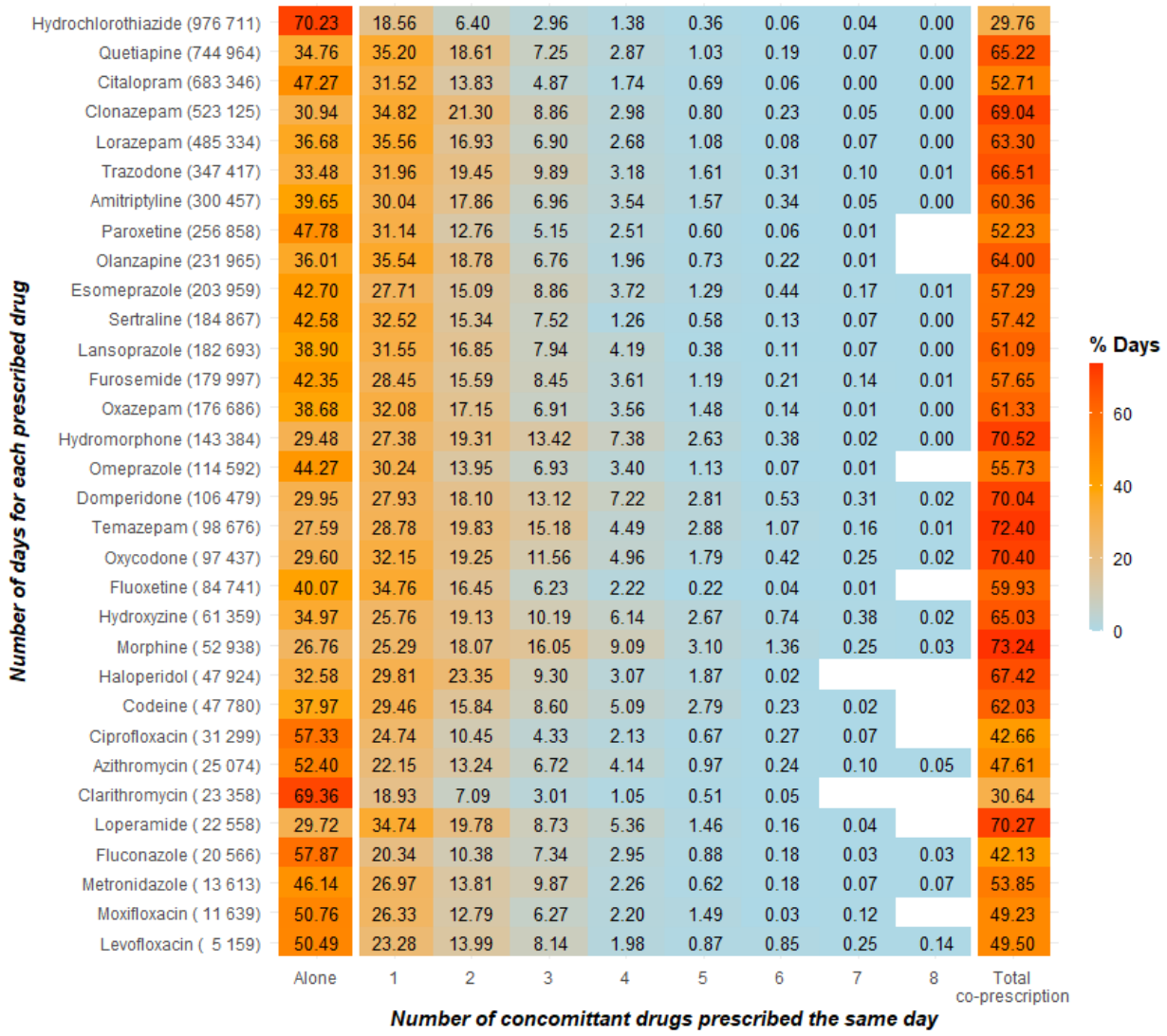

Figure 5-3. Heatmap of drug co-exposure itemsets for drugs involved in the most prevalent DDI among non-elderly community-dwelling adults covered by the public drug insurance of Quebec.

The spectrosome shows the connection among 32 drugs and highlights which co-exposures could lead to a DDI (Figure 4). For example, levofloxacin was found isolated as its proportion of co-exposure was lower than for the other drugs. Conversely, quetiapine was found in combinations with 20 other distinct drugs. Among the 203 drugs-connections, 93 of them were considered as a co-exposure predicted to lead to a DDI, involving 25 out of the 28 drugs presented on the network. The tree presents the details about these most prevalent combinations (Figure S3), each branch

presenting a combination of two or more drugs. Most of the prevalent co-exposures were the consequence of both family physician and specialist prescriptions.

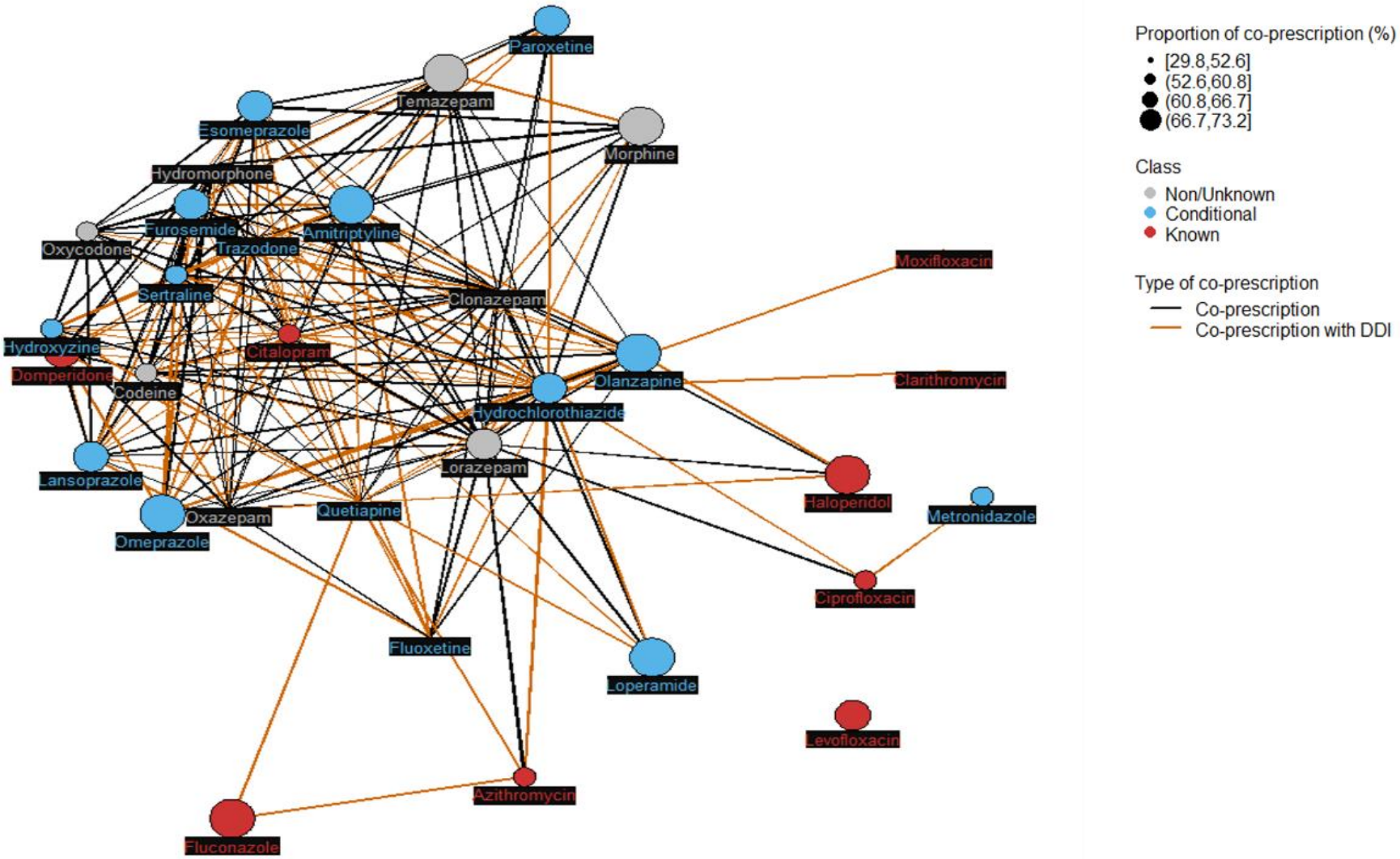

Figure 5-4. Network analysis with frequent itemset mining displaying the co-exposure patterns among the drugs involved in the most prevalent DDI.

Spectrosome of drug-drug interactions. Nodes represent drugs, with the color indicating the risk of causing torsades de pointe (gray: non known risk of Torsades de pointe; blue: conditional risk; red: known risk).

5.7 Discussion

Patients' exposures to harmful drug-drug interactions represent a preventable source of medication errors. As prescription volumes continue to increase, the prevention of avoidable medication errors needs attention: a recent systematic review found that among patient safety incidents occurring in primary care, those associated with diagnosis or medication errors were the most likely to result in patient harm.[42]

One in 8.5 (11.7%) community-dwelling non-elderly adults in Quebec covered by the provincial drug insurance were exposed to at least one high-priority DDI between April 1, 2015 and March 31, 2016; incident cases of exposure represented 35.9% or 2,695 of these. To our knowledge, this is the first study measuring the prevalence and yearly cumulative incidence of exposure to DDI among community-dwelling, non-elderly adult Canadians.

The network analysis tree revealed that drugs leading to exposure to DDI in this study were prescribed by a combination of family physicians and specialists (Figure S3). The heatmap of relative frequencies for each drug involved in the most frequent DDI showed that the drugs involved in the most prevalent DDI are found in combination with one to 9 additional drugs overlapping on the same day (Figure 3); the tree demonstrates the variety of potential combinations of drugs. This finding emphasizes the need for drug safety studies assessing the impact to drug combinations, including those predicted to lead to DDI.

The trained SuperLearner model was able to identify individuals at risk for exposure to DDI with high performance using indicators constructed from administrative health databases for prevalent DDI (AUC 0.90, sensitivity 0.52) but performed poorly for incident DDI with an AUC of 0.78 but a sensitivity of 0.0015 (Table S3).

The most important variables predicting the risk of exposure to a DDI in this study pertained to medication use and continuity of care during the washout period (Figure 2). Variables measuring continuity of care, especially of prescriber (all MD and FP only) and pharmacist care, were among the top predictors of exposure to a high-priority DDI. This finding suggests that interventions to prevent high-priority DDI among community-dwelling non-elderly adults may be most effective when they focus on improving prescriber and pharmacist continuity.

In Quebec family physicians serve as the gatekeepers to specialist care and have a key role in the integration of care for their patients.[43] However, access to a family physician is difficult, specifically for 23% of Quebec residents who are not registered with a family physician.[44] In this context, community pharmacists are already responsible for ensuring safe medication use, [43] and may play an essential role for ensuring safe medication dispensation and consumption because they can integrate and assess the prescriptions from multiple clinicians, especially in the context of fragmented primary care access. A province-wide registry of publicly reimbursed prescription claims was implemented in Quebec in 2013 [45] and became accessible to patients in 2018.

Computerized clinical decision support systems play a key role in the prevention of DDI. However, studies have shown that these systems are largely ignored by clinicians because they generate numerous alerts for DDI which may not lead to increased risk of patient harm.[46, 47] It is thus imperative to identify clinically significant harmful DDI to help guide physicians' prescriptions and the pharmacists' assessment of prescriptions from multiple clinicians, and to improve computerized decision support systems, which will ultimately contribute to prevent patient harm.

5.7.1 Strengths and Limitations:

This study's strengths include the identification of DDI only within overlapping pairs of drugs, the use of provincial administrative claims capturing all dispensations and health services use for a 5% sample of individuals with continuous coverage under the public drug insurance, and the restriction of studied DDI to high-priority DDI. The measurement of different indices of continuity of care through data on outpatient visits, prescribers, pharmacists, pharmacies, and FP-outpatient visits and FP prescribers allowed us to separately assess the effects of each type of continuity of care. The use of SuperLearner allowed us to achieve accurate predictive results for prevalent DDI; further optimization of the SuperLearner could be achieved by tuning the hyperparameters of the machine learning algorithms included in the SuperLearner.[48]

Our study faces six main limitations. First, while some DDI may be prevented through dose modifications, no consideration of dose was made in this study. Second, because we included only individuals with continuous coverage under the public prescription drug insurance, there was an over-representation of individuals with high social and material deprivation index, limiting the generalizability of our findings to all community-dwelling non-elderly adults in Quebec. Third, the assessment of continuity of care at the pharmacy level was potentially inaccurate for 5% of community pharmacies, which changed their legal status over the course of the study period and could not be identified. Fourth, while the assessment of drug exposure using administrative claims databases allows for the accurate assessment of drug exposure, there may be inconsistencies when a drug is prescribed "as needed", where an individual may not be exposed to the drug each day of the stated duration of the prescription claim. This has led to the creation of drug-specific corrective algorithms that are more accurate in their assessment of drug exposure patterns. Because our objective was to assess the overall prevalence of exposure to any high-priority DDI, the number

of included drugs in this study precluded the individual validation of each drug's exposure. Finally, while this study found a high prevalence of exposure to drug-drug interactions among community-dwelling adults, these results do not provide evidence on the actual patient harm in which these exposures may have resulted. Exposure to a high-priority DDI does not always lead to an adverse outcome for the patient. Further studies are needed to identify those DDI leading to patient harm.

5.8 Conclusions

One in nine non-elderly, community-dwelling adults in Quebec was exposed to at least one DDI over 12 months between April 2015 and March 2016, highlighting the importance of careful drug prescribing and dispensation. In addition, drug safety assessments need to consider the impact of exposure to DDI, as many drugs were found in combination with other drugs more often than alone. DDI cases can be accurately predicted using data available in Quebec's administrative health databases and point to a possible involvement of government regulators in the prevention of people's exposure to DDI.

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5.10 Supplemental Material

Table 5-2. 50 Most common DDI among non-elderly adults in Quebec

Object	Precipitant	Claims	Days	N individuals	1-yr Prev
Quetiapine	Citalopram	1163	20228	569	0.89%
Trazodone	Quetiapine	564	8454	341	0.53%
Trazodone	Citalopram	640	13077	327	0.51%
Hydromorphone	Lorazepam	654	5065	305	0.48%
Hydrochlorothiazide	Ciprofloxacin	314	1789	239	0.37%
Metronidazole	Ciprofloxacin	273	2446	236	0.37%
Hydromorphone	Clonazepam	456	3733	209	0.33%
Quetiapine	Hydrochlorothiazide	397	6766	202	0.32%
Hydrochlorothiazide	Citalopram	377	8448	189	0.30%
Sertraline	Quetiapine	374	5934	188	0.29%
Quetiapine	Paroxetine	383	5822	183	0.29%
Quetiapine	Ciprofloxacin	220	1149	180	0.28%
Quetiapine	Olanzapine	269	3041	178	0.28%
Quetiapine	Amitriptyline	327	5321	175	0.27%
Citalopram	Ciprofloxacin	212	1032	167	0.26%
Hydrochlorothiazide	Amitriptyline	289	6207	164	0.26%
Trazodone	Hydrochlorothiazide	299	5797	162	0.25%
Morphine	Lorazepam	305	2458	149	0.23%
Codeine	Lorazepam	243	2150	141	0.22%
Hydrochlorothiazide	Azithromycin	176	807	136	0.21%
Hydrochlorothiazide	Clarithromycin	170	1289	134	0.21%
Citalopram	Amitriptyline	238	4177	131	0.21%
Morphine	Clonazepam	277	1734	130	0.20%
Quetiapine	Esomeprazole	212	3185	127	0.20%
Oxycodone	Lorazepam	341	3008	125	0.20%
Codeine	Clonazepam	268	2186	123	0.19%

Quetiapine	Lansoprazole	223	3516	118	0.18%
Fluconazole	Ciprofloxacin	144	402	117	0.18%
Citalopram	Azithromycin	134	571	113	0.18%
Oxycodone	Clonazepam	250	2649	112	0.18%
Quetiapine	Azithromycin	133	759	108	0.17%
Trazodone	Ciprofloxacin	144	768	108	0.17%
Hydrochlorothiazide	Esomeprazole	216	4695	106	0.17%
Olanzapine	Citalopram	171	2584	106	0.17%
Fluconazole	Citalopram	207	641	101	0.16%
Hydromorphone	Oxazepam	266	2392	101	0.16%
Ciprofloxacin	Amitriptyline	130	768	96	0.15%
Esomeprazole	Citalopram	189	3592	96	0.15%
Trazodone	Paroxetine	209	3836	93	0.15%
Trazodone	Amitriptyline	155	2628	93	0.15%
Moxifloxacin	Hydrochlorothiazide	111	767	92	0.14%
Loperamide	Ciprofloxacin	95	331	91	0.14%
Quetiapine	Fluoxetine	201	3010	91	0.14%
Trazodone	Sertraline	194	3545	90	0.14%
Lansoprazole	Citalopram	169	2958	89	0.14%
Quetiapine	Fluconazole	221	984	89	0.14%
Clarithromycin	Citalopram	99	672	88	0.14%
Metronidazole	Fluconazole	104	362	87	0.14%
Moxifloxacin	Citalopram	109	720	87	0.14%
Quetiapine	Moxifloxacin	110	619	87	0.14%

Table 5-3. Covariates

Type of variables	Variables in model
Demographic (3 variables)	Age, sex, index of social and material deprivation
Multimorbidity (33 variables)	Index of multimorbidity, indicators for presence of 31 chronic conditions, total number of chronic conditions
Continuity of care (21 variables)	Usual provider of care (UPC) and Bice-Boxerman COCI, each one computed for 6 dimensions of continuity (12 total): (1) all MD, (2) FP only, (3) Any prescriber, (4) FP prescriber, (5) pharmacy, (6) pharmacist. Others: Indicator of enrolment with a family physician (FP), indicator of more than one pharmacy, indicator of more than one pharmacist, number of different pharmacists, number of different pharmacies, number of different MD seen, number of different FP seen, number of different prescribers (all MD), number of different FP prescribers
Health Services Use (6 variables)	Number of outpatient visits with all MD, number of outpatient visits with FP, number of days hospitalised, number of ER visits, indicator for at least one ER visit, indicator for at least one hospitalization,
Medication use (5 variables)	Number of different drugs claimed, indicator for 0 or 1 drug claimed, indicator for 2, 3, 4 or 5 drugs claimed, indicator for 6 or more drugs claimed, prior exposure to a DDI.

Table 5-4. Predictive accuracy of the trained ensemble SuperLearner models

Population	AUC test	AUC total	Specificity	Sensitivity
Prevalent DDI	0.9003	0.9484	0.9820	0.5164
Incident DDI	0.7791	0.8412	0.9998	0.0015

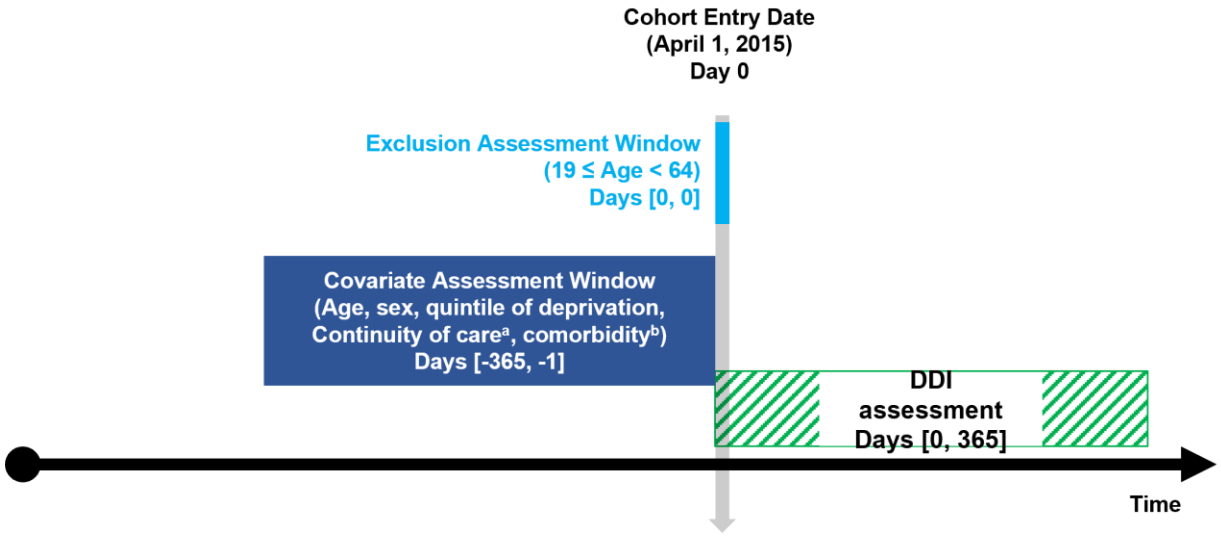


Figure 5-5. Time-based cohort entry study design

Adapted from [49]. (a) Continuity of care was assessed using the Usual provider of care index and the Bice-Boxerman continuity of care index. (b) Indicators for 31 chronic diseases, an index of multimorbidity predicting death and health service use, number of hospitalizations, number of medical visits, number of prescription drugs claimed at least once, number of pharmacies and number of hospital days, number of distinct prescription drugs used, number of diagnoses, and number of physician visits

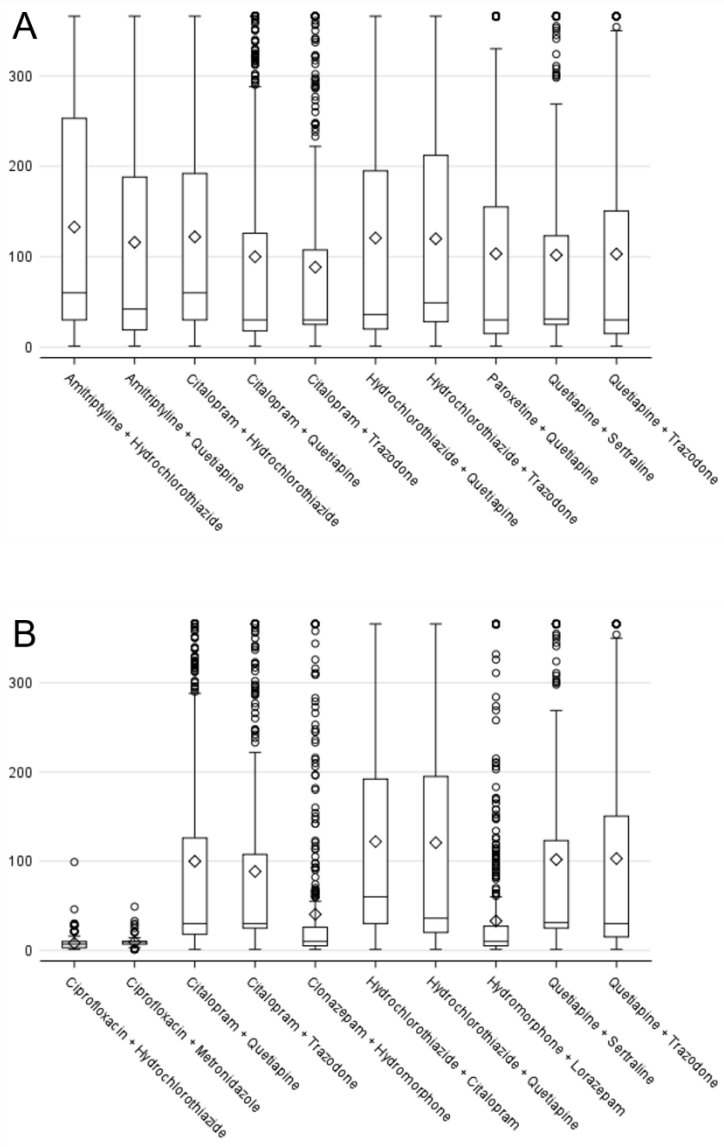


Figure 5-6. Duration in days of episodes of exposure to the 10 most prevalent DDI in 2015.

A. Duration of most prevalent DDI by days of exposure; B. Duration of most prevalent DDI by number of individuals. The horizonal line inside the boxplot represents the median value, while the diamond represents the mean duration, and the upper and lower borders of the box represent the 25th and 75th percentile respectively

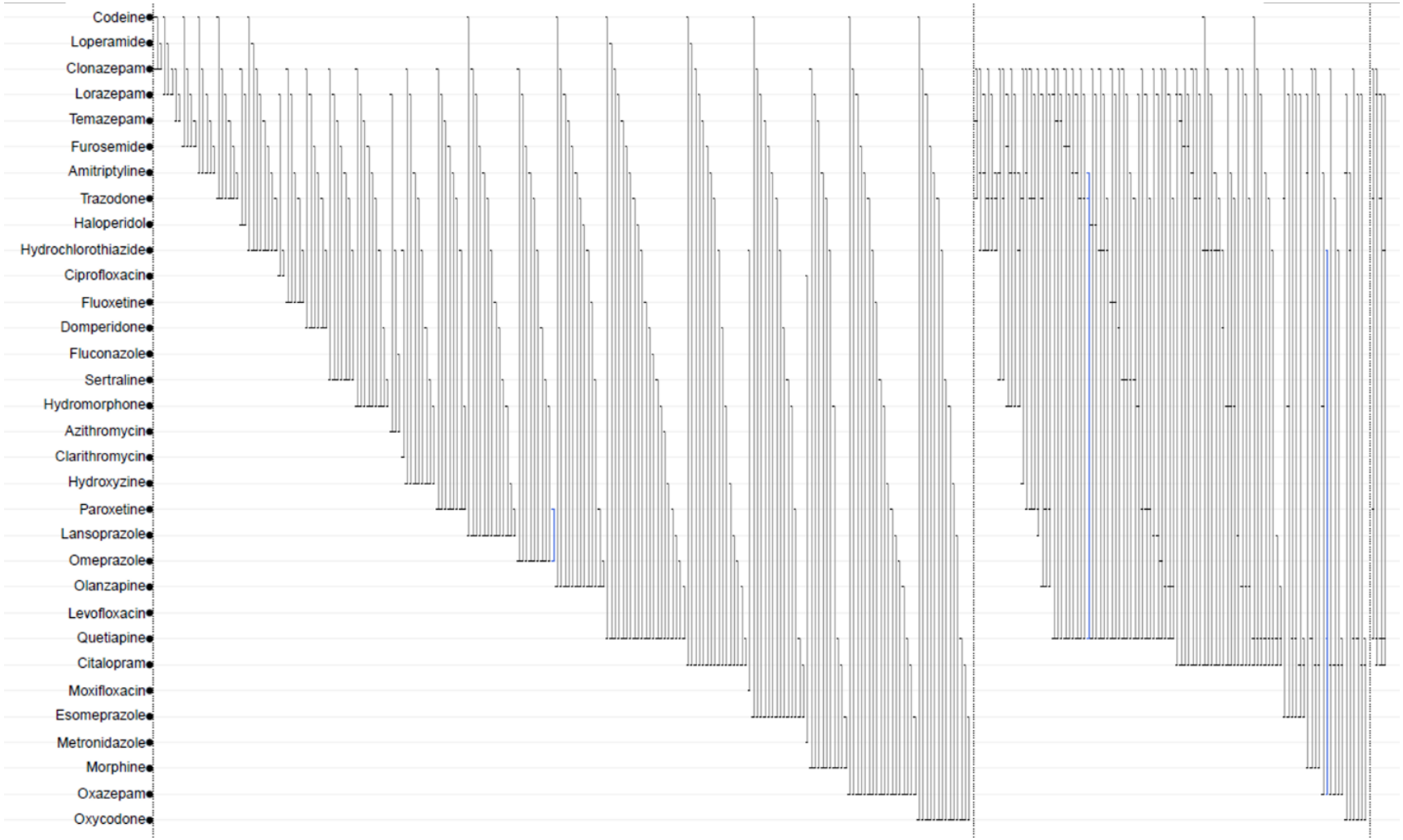


Figure 5-7. Co-exposure tree of the most prevalent drug-drug interactions.

Each branch represents a combination of two or more drugs. The color of the branch identifies if the co-prescription was induced by family physicians (blue), specialits (green) or combinations of both (black).

CHAPTER 6: Using administrative health databases to identify which drug-drug interactions are associated with an increased risk of patient harm among community-dwelling, non-elderly adults in the Canadian province of Quebec (Manuscript 3)

6.1 Preface

Studies measuring exposure to drug-drug interactions, such as the one presented in Manuscript 2, present measurements of exposure to drug-drug interactions with unknown validity for predicting patient harm resulting from these exposures. A recent study found that 6.9% of adult patients (age range 20 – 96, mean age 61.0 ± 15.7) exposed to a drug-drug interaction experienced an adverse event, and 93.1% did not.[1] Despite this, a recent study identified exposure to drug-drug interactions as the possible or probable cause for 5.4% of hospital admissions in a hospital in England over one month.[2] If this rate is true in Canada, admissions due to exposure to drug-drug interactions represents a higher proportion of all hospitalizations than COVID-19 (1.8% in 2020-2021) and acute myocardial infarction (2.4% in 2020-2021) combined.[3]

A leading challenge in the prevention and study of drug-drug interactions is the poor quality of evidence used to generate clinical drug-drug interaction alerts. The perception that alerts are not clinically relevant leads to alert fatigue among clinicians, which in turn leads to a high rate of overridden alerts. [1, 4] Conversely, patients may be deprived of beneficial drugs due to fear of harm from exposure to drug-drug interactions which may not be clinically relevant.

As an embedded CIHR-funded Health systems fellow at Quebec's National Institute for Excellence in Health and Social Services (INESSS), I sought to assess whether the provincial administrative health databases can be used to assess the association between exposure to highly prevalent high-priority drug-drug interactions and the risk of an adverse event. This would allow

for the routine evaluation of the preventable patient harm due to exposure to drug-drug interactions in the province of Quebec, and guide prevention efforts.

The results from Objective 2 allowed me to select a small number of highly prevalent drug-drug interactions to investigate further. Among highly-prevalent drug-drug interactions with a well-documented mechanism, I chose to focus on drug-drug interactions involving the mechanism-based inactivation of cytochrome P450 enzymes 2C19 and 34A by long-term exposure to proton pump inhibitors (perpetrator drugs) and drugs which are metabolised via these enzymes and known to lead to dose-dependent QT prolongation.

Using survival analysis with time-dependent drug exposures, I assessed the dose-dependent daily hazard ratio of exposure to each of four drug-drug interactions and the risk of experiencing an adverse event.

This manuscript is in preparation for submission.

Measuring the association between exposure to four common drug-drug interactions and the hazard of an adverse even among community-dwelling, non-elderly adults in the Canadian province of Quebec

6.2 Abstract

Background: Drug-drug interactions (DDI) are a preventable source of adverse drug effects. Exposure to high-priority DDI is prevalent among community-dwelling adults in the province of Quebec. Whether this exposure leads to increased risk of patient harm remains unknown. Administrative health databases with drug claims data can be leveraged to conduct post-marketing assessment and monitoring of adverse events following exposure to DDI.

Objectives: To investigate whether Quebec administrative health databases held by the Quebec institute for excellence in health and social services can be used to measure increased risk of patient harm (ER visits, hospitalizations, or death) following exposure to high-priority DDI.

Methods: We conducted a retrospective cohort study using provincial administrative health databases on a random sample of 5% of all community-dwelling adults aged 19-64 years on April 1, 2015, with continuous coverage by the public drug insurance between April 1, 2014, and March 31, 2017. Individuals exposed to one of eleven drugs of interest were followed from the first day of exposure to a drug of interest for up to 24 months or until a visit to the emergency department, a hospitalization, or death. Cox proportional hazards with time-varying drug exposures were conducted to assess the dose-dependent association between exposure to one of four drug-drug interactions (proton pump inhibitors + citalopram, proton pump inhibitors + domperidone, proton pump inhibitors + quetiapine, and proton pump inhibitors + ciprofloxacin). Three definitions of

time-varying drug exposure were used: current use, cumulative dose of past seven days, and cumulative dose of past 30 days.

Results: Current exposure to the three drug combinations expected to lead to increased risk of QT prolongation was associated with increased hazard of experiencing an adverse event. The marginal hazard ratios (95% CI) for each added defined daily dose of victim drug in the presence of one defined daily dose of proton pump inhibitor were 1.66 (1.36 – 2.01), 1.76 (1.21 -2.56) and 1.40 (1.03 – 1.77) for citalopram, domperidone, and ciprofloxacin, respectively. Exposure to proton pump inhibitors and quetiapine was not associated with an increased hazard for an adverse event (current use HR 1.09, 95% CI: 0.66 – 1.78). These results suggest that administrative health databases can be leveraged for the routine assessment of patient safety following exposure to DDI.

Conclusion:

Administrative health databases represent a rich source of prescription drug use data that can allow regulators to monitor patient harm following exposure to DDI.

6.3 Introduction

Drug-drug interactions (DDI) are a known preventable source of adverse drug events, estimated to account for 5.4% of hospitalizations.[2] As prescription rates have increased in recent decades, clinicians must rely on computerized decision support systems to identify drug combinations that may lead to a DDI.

Clinical decision support systems (CDS) have been developed and integrated to computerized provider order entry systems to help clinicians prevent their patients' exposure to DDI.[5] These systems display an alert whenever a drug combination predicted to lead to a DDI is prescribed to a patient. However, the full potential of CDS DDI alert systems has not been fully realized, as alert fatigue leads clinicians to override safety alerts.[4, 5] CDS alerts for DDI are most often overridden, including those for the highest predicted severity of harm.[1, 6, 7] Alert fatigue, caused by low specificity for clinically-relevant DDI, was identified in a systematic review as the most important reason for overriding alerts.[4] Alert overriding and subsequent patient exposure to a DDI is potentially appropriate if the benefit of the drugs involved in the DDI is considered greater than the risk of harm from the DDI. However, the low signal-to-noise ratio of the DDI alerts makes it likely that clinicians will override clinically significant DDI alerts. Among multiple types of drug safety alert overrides, a study found that DDI alerts were most likely to be inappropriately overridden.[7] Inappropriately overridden DDI alerts were shown to lead to increased risk for adverse drug events (ADE identified in 4.3% of appropriate overrides vs. 9.4% for inappropriate overrides).[1] Focusing alerts on clinically-relevant DDI may improve their acceptance by clinicians.[5] Alerts were more likely to be effective at preventing patient harm if the patient was part of a high-risk group or if the alert was considered clinically significant.[5]

An improvement of the quality and transparency of the information on which DDI CDS systems are based is needed.[8, 9] Currently, CDS DDI systems are largely based on *in vitro* data required by government regulators as part of the drug approval process, case reports, and small clinical studies.[9] Commercial DDI CPS system vendors construct their own algorithms for identifying DDI. As a result, DDI knowledge sources differ greatly in their classification of drug combinations as potential DDI, as well as on the level of expected severity attributed to the DDI. [10, 11] The performance of commercial CDS systems at predicting clinically significant DDI is not openly shared. The opacity of these data sources leads to clinical confusion and further alert fatigue, in addition to hindering scientific research. [12] Systematic reviews assessing the improvement of safe prescribing following DDI CDS implementation show little to no improvement on patient safety. [5, 13]

In recognition of this problem, the U.S. Office for the national coordinator for health created a consensus-based list of high-priority DDI to be included in all DDI CDS systems.[14] In addition to these consensus-based recommendations, the open, routine identification of DDI leading to patient harm using real-world evidence would greatly help improve the quality of the information included in DDI CDS systems.[9]

Administrative health databases have proven to be a reliable source of information on the real-world use of prescription drugs, including dose and duration of exposure.[15, 16] Canadian administrative health data linking prescription drug use with medical visits, visits to the emergency department, hospitalizations, and deaths, represent a rich source of data for monitoring the effects of DDI exposure on patients.

Regulators tasked with assessing post-marketing drug safety usually rely on spontaneous adverse event reporting systems and information provided by the pharmaceutical drug sponsor. The

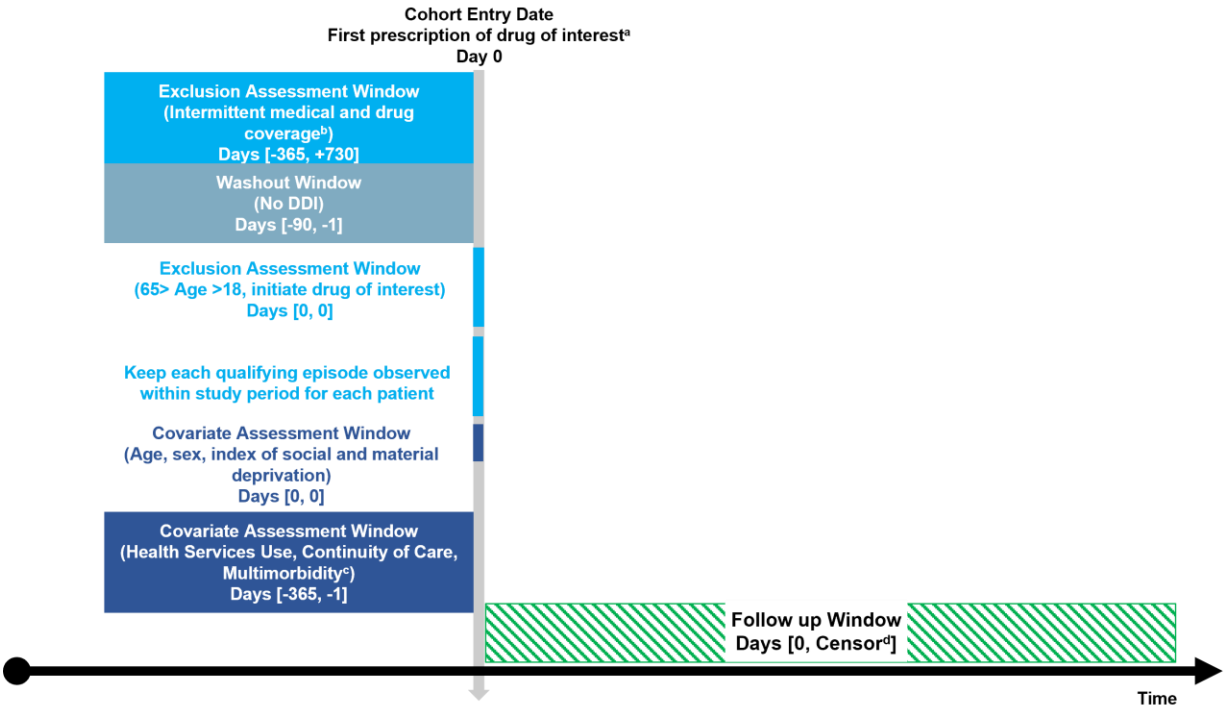
Quebec National Institute for Excellence in Health and Social Services (INESSS) included the assessment of the frequency and impact of common DDI as part of their triennial activity plan (2019-2022)[17] in recognition of the potential for patient harm resulting from exposure to DDI.

Our objective was to assess whether survival analysis using time-varying drug exposures can be used to assess the impact of exposure to DDI on the risk of experiencing an adverse outcome (death, ER visit, or hospitalization) among non-elderly, community-dwelling adults in Quebec. We used provincial administrative databases held by INESSS to conduct four case studies to demonstrate the approach, using the drug combinations: (1) proton pump inhibitors + citalopram or escitalopram, (2) proton pump inhibitors + quetiapine, (3) proton pump inhibitors + domperidone, and (4) proton pump inhibitors + ciprofloxacin.

6.4 Methods

6.4.1 Study design and setting

A longitudinal retrospective cohort study was conducted using administrative health databases of the Canadian province of Quebec. The Quebec public health insurer (RAMQ, Régie de l'assurance maladie du Québec) administers public health and drug insurance plans in the province. The public drug insurance covers individuals without access to private prescription drug insurance, such as self-employed professionals, and those in need of social assistance. RAMQ databases documenting pay-per-act medical consultations, hospitalizations and prescription drug claims of individuals covered by the public drug insurance between April 1, 2014 and March 31, 2017 were used. The study period extended for up to two years from April 1, 2015 to March 31, 2017, and the baseline assessment period covered between April 1, 2014 and March 31, 2015. Figure 1 shows the study design.[18]



a. Treatment episodes defined by date of dispensation and days supply with a stockpiling algorithm if a new dispensation occurs before the end of days supply.
b. Only individuals with continuous coverage by the public drug insurance plan between 2014-04-01 and 2017-03-31 were included
c. Baseline variables included 31 chronic conditions
d. Earliest of: outcome of interest (death or hospitalization), 730 days of follow-up, end of the study period

DDI = Drug-drug interaction

Figure 6-1. Exposure-based cohort entry study design.

6.4.2 Participants

The source population [19] for this study consisted of 5.1 million community-dwelling adult residents (aged 19 to 64 years on April 1, 2015) of Quebec. The database population included 1.2 million individuals with continuous coverage under the public drug insurance of Quebec between April 1, 2014, and March 31, 2017. A random sample of 5% of the database population was extracted. Individuals who resided in long-term care facilities (nursing homes, rehabilitation) were excluded.

The study population consisted of an exposure-based cohort of individuals exposed to at least one of a proton pump inhibitor (omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, dexlansoprazole), or at least one of the victim drugs: citalopram, escitalopram, domperidone, quetiapine, or ciprofloxacin during the study period. Individuals were followed from the first day of exposure to one of the drugs of interest for up to two years, until the first of an adverse event or the study's end. Only individuals who were not exposed to the DDI of interest in the 90 days washout period preceding the index drug exposure were included in the analysis.

6.4.3 Variables

Baseline characteristics were assessed during the 12-month period preceding the study's start date. These were age, sex, index of social and material deprivation,[20] index of comorbidity,[21] and enrolment with family physician.

All drug products were converted to individual active ingredients (subsequently, drugs). Individuals' daily exposure to each drug was assessed from claims data containing the amount dispensed and duration of treatment for each dispensed drug product. Individuals were assumed to be exposed to the drug starting on the day of dispensation and for the duration specified in the claim. Oversupplies of each drug were carried forward and allowed to fall outside of the study period. Drug dose information included in each claim was used to calculate the number of defined daily doses[22] for each drug for each day of follow up.

We created a composite outcome for adverse events including the first of a visit to the emergency department, a hospital admission (excluding all non-urgent admissions and day surgeries), or death. We excluded individuals for whom the outcome occurred on the same day as the index drug claim to avoid the possibility that the outcome (e.g., a visit to the emergency department) preceded

exposure to the index drug. We included all ER visits and urgent hospitalizations regardless of the main diagnostic codes, as adverse drug events are often missed in these settings [23] and unlikely to be captured in administrative codes. [16, 24] ER visits resulting in hospitalization were counted as a single event.

DDI investigated

Proton pump inhibitors are a class of drugs used to treat gastric acid-related conditions. Six PPI are used in Quebec: omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole. These PPI inhibit the activity of cytochrome P450 enzymes CYP2C19 and CYP3A4 to varying degrees. [25, 26] Omeprazole is known to lead to the inhibition of cytochrome P450 enzyme CYP2C19 and CYP3A4,[27, 28] leading to a clinically-relevant DDI with the antiplatelet clopidogrel.[29]

We assessed exposure to four potential DDI involving PPI as the perpetrator drug: (1) PPI + citalopram/escitalopram, (2) PPI + domperidone, (3) PPI + quetiapine, and (4) PPI + ciprofloxacin. An individual was considered exposed to one of the four DDI of interest on any given day if the product of the doses of the two drugs involved in each DDI was larger than zero on that day.

Citalopram and its s-enantiomer escitalopram are selective serotonin reuptake inhibitors metabolized mainly by the action of CYP2C19. We expected that co-exposure to PP + citalopram or escitalopram would lead to increased risk of long QT due to increased exposure to citalopram or escitalopram.[30]

The antipsychotic quetiapine and prokinetic domperidone, both metabolized by CYP3A4, are known to lead to dose-dependent QT prolongation.[31] The inhibition of CYP3A4 by PPI could

lead to higher plasma concentration of these drugs, with increased risk of prolongation of the QT interval and subsequent increased risk of a cardiac adverse effect.

Finally, the antibiotic ciprofloxacin is well known to lead to long QT and increased risk of cardiac adverse effects.[31] Ciprofloxacin is not metabolized by CYP2C19 or CYP3A4[32] and as such PPI would not be expected to increase ciprofloxacin plasma concentrations. On the contrary, PPI in combination with certain formulations of ciprofloxacin leads to decreased ciprofloxacin absorption.[33]

6.4.4 Data Sources

The Quebec public health insurer (RAMQ) and the Ministry of Health and Social Services maintain health services and drug insurance databases, to which INESSS has access to fulfil its mandates. We extracted demographic (age, sex, index of social and material deprivation), medical service use (date of medical consultation, main ICD-10 diagnostic codes, type of establishment, physician specialty), and medication claims (date, duration, daily dose, prescriber type, prescriber specialty, pharmacy establishment) each participant. The date of all emergency room (ER) visits was extracted from the provincial emergency room database (BDCU). Date of hospital admission, reason for admission, and main diagnostic codes associated with the admission were extracted from the hospitalizations database (MED-ECHO).

6.4.5 Analytical methods

Daily exposure to the drugs of interest was modeled using three different time-varying definitions: current dose, cumulative dose of the past 30 days, and cumulative dose of the past 7 days. We computed event rates using person-days of exposure for each drug and DDI; R package “epitools”

(version 0.5-10.1)[34] was used to compute 95% confidence intervals for the rates using the exact method.

Cox proportional and non-proportional hazards regressions were used to analyze the association between exposure to the drugs of interest and an outcome. The proportionality assumption was assessed, and an interaction term including the length of the time interval was added to correct for any violations.

We used the SAS (9.4) procedure PHREG with the 'hazardratio' statement to assess the interaction between the drugs of interest at different doses of each interacting drug. We computed the natural logarithm of the resulting hazard ratios with Wald 95% confidence intervals to construct dose-specific linear equations, which enabled us to compute the expected hazard ratios and 95% CI at each dose of the interacting drugs. The R package 'pheatmap' [35] was used to create heatmaps presenting the hazard ratios and 95% confidence intervals at each dose of each interacting drug.

Using the current use models, the resulting hazard ratios were used to approximate the daily risk ratio of an adverse event upon exposure to each drug alone and in combination with the interacting drug and compute the multiplicative interaction using the relative excess risk due to interaction (RERI).[36] This is a measure of whether the combined effect of the drugs is greater than the product of their effect.[37]

6.5 Results

6.5.1 Participants

A total of 11 121 incident users to one of the drugs of interest were identified (Figure 2). Participant characteristics are summarized in Table 1.

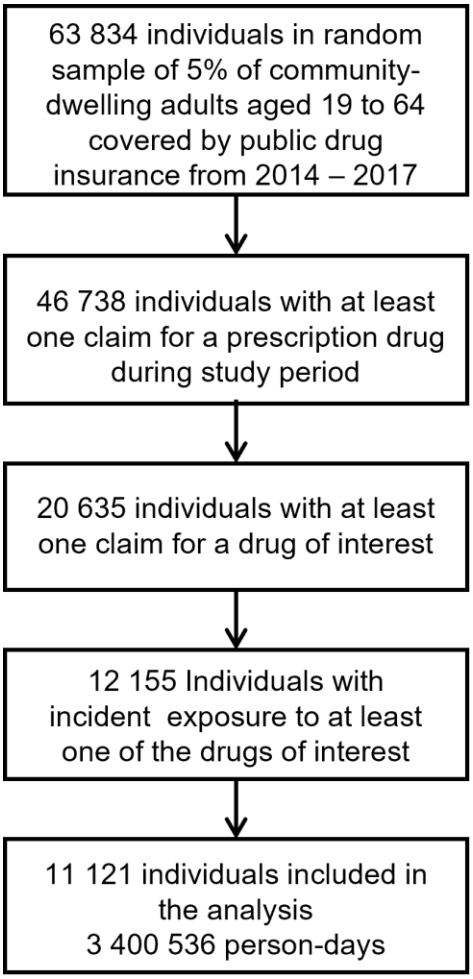


Figure 6-2. Flowchart of study population

Table 6-1. Participant characteristics

Covariate	Exposed to PPI	Exposed to victim	PPI x Victim
DDI 1: PPI + Citalopram/escitalopram			
Female sex, N (%)	3788 (59.2)	829 (66.5)	110 (67.9)
Age, mean (SD)	48.9 (12.0)	41.7 (8.0)	45.6 (8.3)
Comorbidity index, mean (SD)	0.16 (0.82)	0.10 (0.32)	0.18 (0.40)
Index deprivation, N (%)			
1	731 (11.4)	141 (11.3)	19 (11.7)
2	1043 (16.3)	200 (16.1)	27 (16.7)
3	1211 (18.9)	206 (16.5)	22 (13.6)
4	1526 (23.8)	324 (26.0)	46 (28.4)
5	1819 (28.4)	361 (29.0)	48 (29.6)
missing	72 (1.1)	14 (1.1)	0
DDI 2: PPI + Domperidone			
Female sex, N (%)	3788 (59.2)	166 (77.2)	65 (67.7)
Age, mean (SD)	48.9 (12.0)	46.7 (1.83)	49.9 (12.1)
Comorbidity index, mean (SD)	0.16 (0.82)	0.14 (0.07)	0.22 (0.75)
Index deprivation, N (%)			
1 (lowest deprivation)	731 (11.4)	28 (13.0)	12 (12.5)
2	1043 (16.3)	29 (13.5)	13 (13.5)
3	1211 (18.9)	37 (17.2)	14 (14.6)
4	1526 (23.8)	51 (23.7)	27 (28.1)
5 (highest deprivation)	1819 (28.4)	70 (32.6)	30 (31.3)
missing	72 (1.1)	0	0
DDI 3: PPI + Quetiapine			
Female sex, N (%)	3788 (59.2)	522 (50.4)	66 (51.6)
Age, mean (SD)	48.9 (12.0)	42.1 (13.1)	47.02 (12.5)
Comorbidity index, mean (SD)	0.16 (0.82)	0.10 (0.49)	0.25 (1.04)
Index deprivation, N (%)			
1 (lowest deprivation)	731 (11.4)	105 (10.1)	9 (7.0)
2	1043 (16.3)	148 (14.3)	18 (14.1)
3	1211 (18.9)	193 (18.7)	25 (19.5)
4	1526 (23.8)	258 (24.9)	36 (28.1)
5 (highest deprivation)	1819 (28.4)	316 (30.5)	40 (31.3)
missing	72 (1.1)	15 (1.5)	0
DDI 3: PPI + Ciprofloxacin			
Female sex, N (%)	3788 (59.2)	2551 (71.5)	147 (67.7)
Age, mean (SD)	48.9 (12.0)	46.0 (13.9)	50.5 (12.4)
Comorbidity index, mean (SD)	0.16 (0.82)	0.14 (0.61)	0.29 (1.01)
Index deprivation, N (%)			
1	731 (11.4)	514 (14.4)	20 (9.2)
2	1043 (16.3)	690 (19.3)	33 (15.2)
3	1211 (18.9)	717 (20.1)	46 (21.2)
4	1526 (23.8)	810 (22.7)	60 (27.7)
5	1819 (28.4)	807 (22.6)	57 (26.3)
missing	72 (1.1)	30 (0.8)	1 (0.5)

6.5.2 Main Results

During the 3,400,536 person-days of follow-up (median 276, IQR 393 person-days), 4114 events were recorded, for a rate of 121 events per 100,000 person-years of follow-up (95% CI: 117 – 125).

DDI 1: PPI + citalopram/escitalopram

Co-exposure to PPI and citalopram was associated with an increased hazard for the event using the three time-varying definitions of drug exposure.

In the current use time-varying model, co-exposure to PPI and citalopram/escitalopram led to an estimated hazard ratio of 1.66 (95% CI: 1.36 – 2.01) per day for each increase of one unit in the product of the drugs' doses.

In the absence of any PPI, each one-unit increase in defined daily dose of citalopram/escitalopram was not associated with an increased hazard for the event (HR 0.97 [0.86-1.09]). In the presence of any PPI, the estimated hazard ratios associated with a one-unit increase in citalopram or escitalopram are 1.19 (1.06-1.35), 1.47 (1.22-1.77), and 2.22 (1.55-3.18) for PPI DDD values of 0.5, 1, and 2, respectively. The hazard ratio estimates for each value of defined daily doses of the drugs of interest is presented in Figure 3.

The model using cumulative dose of the past 30 days resulted in an estimated hazard ratio of 1.0003 (95% CI: 1.000 – 1.001) for each one unit increase in the product of the drugs' doses. In the absence of any PI exposure in the past 30 days, each one-unit increase in citalopram/escitalopram exposure was associated with a hazard ratio of 1.00 (0.996-1.004). In the presence of any PPI in the previous 30 days, the estimated hazard ratios associated with a one-unit increase in the defined daily dose of citalopram or escitalopram exposure were 1.005(1.00 – 1.01),

1.01(1.002-1.018), and 1.02(1.003-1.037) for cumulative PPI doses of 15 (corresponding to 0.5 defined daily doses of PPI per day for 30 days preceding the index citalopram/escitalopram dose), 30, and 60, respectively.

Finally, the modeling of drug exposure as the cumulative dose of the past seven days revealed a marginal hazard ratio of 1.005 (95% CI: 1.001 – 1.009, p=0.0076) for each one unit increase in the product of the drug doses. In the absence of any PPI exposure in the past 7 days, each one-unit increase in citalopram or escitalopram defined daily dose is associated with a hazard ratio for the event of 0.995 (0.980 – 1.010). In the presence of any PPI in the 7 days preceding the index citalopram or escitalopram exposure, the hazard ratios associated with a one-unit increase in citalopram or escitalopram exposure were 1.013 (0.996 – 1.030), 1.021 (1.001 – 1.041), and 1.074 (1.019-1.133) for cumulative PPI defined daily doses of 3.5, 5, and 14, respectively.

The analysis of multiplicative interaction yielded a RERI of 1.38 (95% CI 1.32 – 1.44), indicating the presence of a multiplicative interaction of the association of each drug on the daily hazard of an adverse event.

DDI2: PPI + domperidone

Co-exposure to PPI and domperidone was associated with an increase in the hazard only in the current use exposure models, but no association was found when the cumulative exposure definitions were used.

In the current use time-varying model, co-exposure to PPI and domperidone led to a hazard ratio of 1.76 (95% CI: 1.21 – 2.56) per day for each increase of one unit in the product of the drugs' doses.

In the absence of any PPI, each one-unit increase in defined daily dose of domperidone was not associated with an increased hazard for the event (HR 0.806 [0.539-1.206]). In the presence of any PPI, the hazard ratios associated with a one-unit increase in domperidone were 1.070 (0.767-1.493), 1.419 (0.990-2.035), and 2.499 (1.351-4.621) for PPI DDD values of 0.5, 1, and 2, respectively. The conditional hazard ratio estimates for each value of defined daily doses of the drugs of interest is presented in Figure 3.

When exposure to the drugs of interest was modeled as the cumulative exposure (of the past 30 days, and of the past 7 days), co-exposure to domperidone and PPI was not associated with an increase hazard ratio for the event. In the cumulative dose of the past 30 days model, the marginal hazard ratio for the event associated with co-exposure to any PPI and domperidone was 1.001 (95% CI 1.000 – 1.001). In the absence of any PPI exposure in the past 30 days, an increase in one DDD of exposure to domperidone was associated with a hazard ratio for the event of 0.990 (0.973-1.008). In the presence of any PPI exposure in the past 30 days, a one-unit increase in exposure to domperidone was associated to hazard ratios of 1.086 (0.989-1.193) and 1.197 (0.984-1.455) for cumulative PPI doses of 15 and 30, respectively. Finally, in the presence of any PPI in the past 7 days, each one-unit increase in domperidone exposure was associated with hazard ratios of 1.008 (0.966-1.052), 1.018 (0.974-1.064), and 1.086 (0.989-1.193) for cumulative PPI DDD of 3.5, 5, and 15, respectively.

The multiplicative RERI of exposure to PPI and domperidone was 1.61 (95% CI 1.51 – 1.71), indicating the presence of a multiplicative interaction of the association of each drug on the daily hazard of an adverse event.

DDI3: PPI + quetiapine

Co-exposure to PPI and quetiapine was not associated with an increase in the hazard in the current use exposure models (HR 1.09, 95% CI: 0.66 – 1.78) per day for each increase of one unit in the product of the drugs' doses.

In the absence of any PPI, each one-unit increase in defined daily dose of quetiapine was not associated with an increased hazard for the event (HR 1.447 [0.961-2.178]). In the presence of PPI, the hazard ratios associated with a one-unit increase in quetiapine defined daily dose were 1.527 (1.072 – 2.174), 1.611 (0.737 – 3.552), 1.701 (0.475 – 0.302) and 1.795 (0.302 – 10.65) for PPI DDD values of 1, 2, 3, and 4, respectively. The conditional hazard ratio estimates for each value of defined daily doses of the drugs of interest is presented in figure 4.

No association was found when the cumulative exposure definitions were used in the cumulative dose of past 30 days model (HR 1.00, 95% CI: 0.999 – 1.001), or in the in the cumulative dose of past 7 days model (HR 1.002, 95% CI: 0.993 – 1.011)

The multiplicative interaction RERI for PPI and quetiapine was 0.96 (95% CI 0.89 – 1.04), indicating the absence of a multiplicative interaction of the association of each drug on the daily hazard of an adverse event.

DDI4: PPI + ciprofloxacin

The current use model revealed a marginal hazard ratio of 1.40 (1.03 – 1.77) per day of exposure for each one-unit increase in the product of the defined daily doses of both drugs.

In the absence of any PPI, an increase in of defined daily dose of ciprofloxacin was associated with a hazard ratio for the event of 2.80 (95% CI 2.30 – 3.39). In the presence of PPI on the same day, the hazard ratios associated with a one unit increase in the defined daily dose of ciprofloxacin were 3.30 (2.63 – 4.14), 3.90 (2.71 – 5.62), and 5.45 (2.68 – 11.05) for PPI doses of 0.5, 1, and 2, respectively.

When the drug exposure was modeled as the cumulative dose of the past 30 days, co-exposure to ciprofloxacin and PPI was not associated with an increased hazard for the event (HR 1.0004[0.999 – 1.002], p = 0.5977). In the absence of any PPI exposure in the past 30 days, each unit increase in defined daily dose of ciprofloxacin in the past 30 days was associated with a hazard ratio of 1.028 (1.009 – 1.048). In the presence of PPI, exposure to ciprofloxacin in the past 30 days was associated with hazard ratios of 1.034 (1.010 – 1.058), 1.040 (0.999 – 1.082), and 1.051 (0.972 – 1.137) for cumulative PPI DDD of 15, 30, and 60, respectively. When the drug exposure was modeled as the cumulative exposure in the past seven days, co-exposure to any PPI and ciprofloxacin in the past 7 days was associated with a hazard ratio for the event of 1.008 (0.999 – 1.017). In the absence of any PPI, exposure to ciprofloxacin in the past 7 days was associated with a hazard ratio of 1.079 (1.037 – 1.121). In the presence of PPI, exposure to each additional unit of ciprofloxacin was associated with a hazard ratio of 1.108 (1.063 – 1.155), 1.121 (1.068 – 1.177), 1.212 (1.071 – 1.373) for cumulative PPI doses of 3.5, 5, and 10, respectively.

The multiplicative RERI for PPI and ciprofloxacin was 1.26 (95% CI 1.09 – 1.47), indicating the presence of a multiplicative interaction in the association between exposure to these drugs and an adverse event.

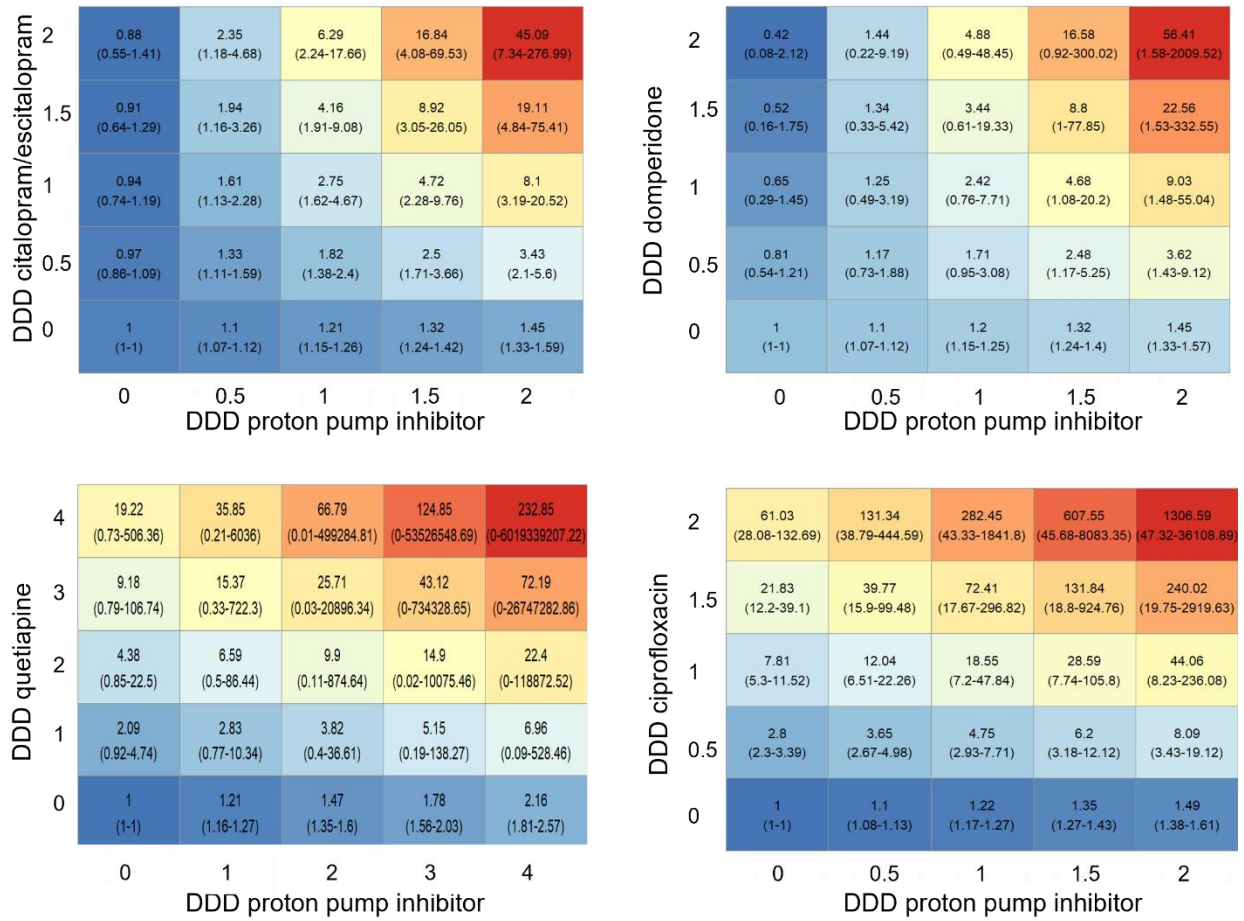


Figure 6-3. Hazard ratio by dose of interacting drugs

Association of covariates and the risk of an adverse event

Each year of increased age resulted in a daily decrease in the hazard for an event, with a HR of 0.989 (0.987-0.991). Compared to those in the lowest quintile of social and material deprivation (i.e., those with the highest socioeconomic status), a higher quintile of social and material deprivation was associated with an increase in the hazard for an event, with hazard ratios of 1.14 (1.007-1.29), 1.24 (1.101-1.399), 1.336 (1.192-1.498), and 1.497 (1.340-1.673) for the second, third, fourth and fifth quintiles respectively. A higher comorbidity score was also associated with an increased daily hazard for the event, with each unit of increase in the comorbidity score

associated with a hazard ratio of 1.026 (1.018 – 1.034). Sex and enrolment with a family physician in the year prior to the study were not significantly associated with the hazard for the event (HR 0.996[0.934 – 1.061, p = 0.8908] and 1.042[0.970 – 1.120, p = 0.2612] for female sex and enrolment with a family physician, respectively).

6.6 Discussion

Calls for improvement of DDI knowledge sources through the transparent use of public, routinely collected databases, including administrative health databases, have been made by experts.[9] Our results are congruent with existing evidence and show promise regarding the use of administrative health databases to identify harmful DDI in Quebec.

We investigated drug combinations between proton pump inhibitors and four victim drugs know to lead to cardiac arrhythmias and sudden cardiac death: citalopram/escitalopram, quetiapine, domperidone, and ciprofloxacin. We found that co-exposure to proton pump inhibitors was associated with an increased hazard for an adverse event due to the increased exposure to citalopram/escitalopram, domperidone, and ciprofloxacin, but not quetiapine. There was evidence of multiplicative interaction in these three DDI. While quetiapine has a known risk of leading to long QT and increased adverse effects, no interaction effect was observed with proton pump inhibitors for the risk of ER visits, hospitalization, or death.

In line with our findings, the combination of PPI with citalopram/escitalopram has previously been linked to increased serum concentrations of citalopram/escitalopram,[38] increased risk of cardiac arrest among the general population[39] and sudden cardiac death among people receiving hemodialysis.[30]

Domperidone use has been associated with increased risk of sudden cardiac death and ventricular arrhythmia.[40] Pharmacokinetic models predict an increase of 27% and 33% in domperidone plasma concentration over time when taken with omeprazole and esomeprazole, respectively;[41] studies evaluating the use of PPI in combination with domperidone for the treatment of gastroesophageal reflux disease found no safety concerns for the combination, but these studies used small numbers of participants (<50 participants treated with PPI + domperidone).[42, 43] Quetiapine has also been linked to increased risk for QT prolongation,[31] sudden cardiac and sudden unexpected death;[44] co-administration of quetiapine with strong inhibitors of CYP3A4 leads to marked increases in quetiapine plasma concentrations.[45] Ciprofloxacin is known to increase the risk of torsades de pointes but its metabolism is not expected to be affected by exposure to PPI.[31, 32]

6.6.1 Strengths and limitations

Our study is the first to attempt to assess the impact of exposure to high-priority DDI using administrative health databases from Quebec among community-dwelling non-elderly adults. The standardized dosing information and assessment of the hazard ratio by daily dose of perpetrator and victim drug allowed us to create easily interpretable heatmaps that may help inform DDI knowledge bases.

Our study presents several limitations. Limitations in sample size for the detection of rare adverse events precluded outcome-specific analyses, and analyses by individual PPI, which have been found to have varying CYP inhibitory potencies.[25] We purposefully kept our outcome definition to include all ER visits, urgent hospitalizations, and deaths because diagnostic codes in the

hospitalization database have low sensitivity,[16] and clinicians do not always recognize adverse drug events as such.

The population included in the study is limited to individuals with continuous coverage under the public drug insurance program of the province of Quebec. Lastly, no attempt was made to use a causal framework to evaluate the impact of the DDI investigated.

6.7 Conclusion

Our findings represent a starting point for the investigation of the impact of DDI using public administrative health databases in Quebec. Given that drug prescribing is the most common medical intervention[46] with the potential for harming many people, and accounting for a large proportion of health expenditures, focus on the prevention of harm from exposure to DDI is of paramount importance for health regulators. Complementing existing information drawn from preclinical data and small clinical studies with transparent assessments of the impact of DDI using real-world evidence can help improve the quality of the information used in DDI CDS systems and reduce alert overrides.

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CHAPTER 7: DISCUSSION

Adverse drug events are a leading cause of patient harm, with an estimated 300,000 Canadians severely or fatally affected each year.[23] Among them, drug-drug interactions are a preventable source of adverse drug events, and as such should be a priority for intervention. Currently, most of the evidence used in drug-drug interaction identification systems originates from pre-clinical *in vitro* assessments, small randomized clinical trials, or spontaneous adverse event reporting systems. While this is essential evidence, I propose that existing publicly owned administrative health databases in Quebec can provide complementary evidence that can help improve the knowledge about drug-drug interactions. The latter can be used to assess the population-wide exposure to drug-drug interactions, predict such exposures, and estimate their impact on patient well-being. This thesis can contribute to improve the routine post-marketing assessment of drug safety conducted in Quebec, and the evidence used to guide clinical practice. In this section, the main results, implications for policy making, limitations and future research are discussed.

7.1 Main results

The general goal of this thesis was to study the frequency and consequences of exposure to drug-drug interactions among community-dwelling, non-elderly adults. Below, I discuss the main findings related to my four specific objectives.

7.1.1 Objective 1: to conduct a knowledge synthesis on the prevalence and rate of exposure to drug-drug interactions among community-dwelling non-elderly adults

The first objective was to estimate the prevalence of exposure to drug-drug interactions among community-dwelling non-elderly adults in different healthcare systems around the world. This was

addressed in Chapter 4 (Manuscript 1) with a systematic literature review and meta-analysis of the prevalence and rate of exposure to drug-drug interactions. The meta-analysis found a pooled prevalence of exposure to drug-drug interactions of 0.18 (95% CI: 0.09 – 0.35, PI: 0.01 – 0.80), and a pooled rate of exposure of 20.12 DDI per 1,000 person-months exposed to two or more drugs (95% CI 7.25 to 55.84 DDI per 1,000 person-months, PI 0.57 – 152.07). These represent wide predictive intervals, e.g., from 1% to 80% prevalence, are indicative of differing settings and methodological choices of the included studies. Despite this heterogeneity, we conducted a random-effects meta-analysis to produce prediction intervals for future research, as recommended in the literature.[138, 139]

Such large heterogeneity of results of included studies has been described in other systematic literature reviews of the prevalence of exposure to drug-drug interactions.[140] For example, Thai *et al* (2016) found that the prevalence of exposure to potential statin-drug interactions ranged from 0.19% to 33% of those individuals using statins.[141] Another systematic literature review found that 60% to 100% of patients undergoing hematopoietic stem cell transplantation were exposed to at least one drug-drug interaction,[142] and a systematic review of the prevalence of exposure to herb-drug interactions among adults aged 65 years or older found a prevalence ranging from 5.3% to 88.3% of people. [143]

A potential source of this heterogeneity is the use of different sources of predicted drug-drug interaction information among the included studies.[140] Poor agreement across sources of information and opacity in the methods used for classifying drug combinations as potential drug-drug interactions lead to different outcomes being assessed in each study that assesses the exposure to drug-drug interactions.

Another source of heterogeneity in these results may stem from differences in the data and methods used to measure drug exposure. Eight of the included studies in our review used administrative health databases, [144-151] and five used prescription records from electronic medical records. [152-156] We identified 16 different sources of information used to assess exposure to drug-drug interactions, with few studies describing the number of drug-drug interactions that were investigated. Another source of heterogeneity in our findings may relate to the wide range of time, as we did not limit our searches by date hoping to evaluate whether there was increased exposure to drug-drug interactions over time. The small number of studies precluded a meta-regression to assess this possible source of heterogeneity.

The remaining three objectives in this thesis were addressed using administrative health databases held by Quebec's public health insurer (*Régie de l'assurance maladie du Québec* RAMQ), and the Quebec Ministry of Health and Social Services (MSSS), which were accessed through the National Institutes for Excellence in Health and Social Services (*Institut national d'excellence en santé et services sociaux*, INESSS).

7.1.2 Objective 2: to measure the exposure to high-priority drug-drug interactions among community-dwelling non-elderly adults in Quebec

The second objective, assessing the prevalence and incidence of exposure to drug-drug interactions among community-dwelling, non-elderly adults in Quebec (Chapter 5, Manuscript 2) was addressed using the prescription claims database of the public drug insurance of Quebec.

I found that 11.7% (95% CI 11.5 – 12.0%, N = 7,498) and 19.1% (18.7 – 19.5%) of all adults with continuous coverage by the public drug insurance of Quebec and among those exposed to two or more drugs, respectively, were exposed to at least one day of overlapping drugs involved in high-priority drug-drug interactions during the fiscal year between April 2015 and March 2016. Among these, 35.9% (34.9 – 37.0%, N = 2,695) of those exposed to a drug-drug interaction were individuals with an incident exposure during the study year.

These results are similar to the pooled prevalence of exposure to drug-drug interactions among non-elderly adults exposed to two or more drugs. We found that 19% (95% CI 18.7%-19.5%) of non-elderly adults in Quebec with two or more drugs were exposed to at least one high-priority drug-drug interaction, whereas our systematic review and meta-analysis (Chapter 4, Objective 1) found a pooled prevalence of 18% (95% CI: 9% - 35%, PI: 1% - 80%) among the included studies. We identified eight studies which were similar to ours in that they used administrative claims databases and presented the prevalence of exposure to drug-drug interactions, [144-151] of which two considered temporally overlapping drug exposures. [146, 151] Bjerrum *et al* (2003) found a prevalence of exposure to at least one major drug-drug interaction of 0.7% (554/78,786) among individuals aged 20 – 59 years old with at least one instance of overlapping drugs in Denmark in 1999. [146] In Italy, Tragni *et al* (2013) found a prevalence of exposure to at least one of 27 major DDI of 9.2% of those individuals aged 0 – 64 years with at least one prescription claim for a drug of interest in 2004- 2005. [151] These two studies share common methods of assessing exposure to drug interactions but were conducted with data from 1999 and 2004-2005. The years since then have been marked by increases in the prescription rates for outpatient adults, with a Scottish study reporting the doubling of the proportion of adults with five or more drugs, and tripling of the proportion of adults with 10 or more drugs between 1995 and 2010. [157] The most recent study

using prescription claims data was completed in Slovenia over 12 months in 2015. [158] Drug pairs were only assessed for the presence of interactions if they were dispensed on the same day. This study found that 12.8% (83,729/652,753) of adults aged 20 to 59 years taking two or more drugs (among a list of 196 victim drugs, unknown number of potential drug-drug interactions) were exposed to at least one clinically relevant drug-drug interaction. This is lower than our finding of 19% exposure to drug-drug interactions among non-elderly adults exposed to two or more drugs. This difference may be due to two main reasons: first is the fact that the study in Slovenia may have included less potential drug-drug interactions (those involving 196 victim drugs), whereas we included 4,395 potential drug-drug interactions. Secondly, the consumption of prescription drugs is higher in Canada than the OECD average, [159] and higher in Quebec compared to the rest of Canada. [160]

7.1.3 Objective 3: to identify demographic and health system variables associated with the subsequent risk of exposure to selected high-priority drug-drug interactions.

The third objective was to assess whether exposure to drug-drug interactions can be predicted from the health system use variables contained in the administrative health databases in Quebec (Chapter 5, Manuscript 2). Using a cutting-edge ensemble machine learning approach, the health system use variables considered were able to predict prevalent DDI exposures over 12 months with an AUC of 0.90, and incident (new) exposures to drug-drug interactions with an AUC of 0.78 on test data. These results suggest that individuals at risk for prevalent exposure to drug-drug interactions can be identified based on demographic, continuity of care and health system use variables constructed from data contained in administrative health databases. While exposure to a

drug-drug interaction does not always lead to an adverse event (an estimated 6.9% of those exposed experience an adverse event)[66] the identification of those individuals at risk may help guide targeted prevention efforts. The identification of the variables most associated with an increased risk of exposure to a drug-drug interaction may help to identify and target the services that have the potential for decreasing exposure to a drug-drug interaction. For example, the number of different pharmacies used and pharmacy continuity during the washout year were relatively important variables in the prediction of exposure to drug-drug interactions, suggesting that prevention efforts may consider targeting pharmacy loyalty. Similarly, the number of prescribers and prescriber continuity appear to be more important at predicting the risk of exposure to drug-drug interactions than age, sex, index of deprivation, comorbidity index, and other variables. This suggests that a strengthening of medication reconciliation efforts in primary care may help prevent exposure to drug-drug interactions. These findings also suggest that age-based limitations on the study of the risk of exposure to drug-drug interactions are not justified.

Other studies using machine learning for the identification of drug-drug interactions have mostly focused on signal detection from drug molecular data, spontaneous adverse event reporting systems, or electronic health records. [53, 161] A systematic review identified one study using sequence symmetry analysis to assess the association between exposure to direct oral anticoagulants and non-bleeding adverse events using French administrative claims data.[162] To our knowledge, no other machine learning approaches have been proposed for the identification of future exposure to drug-drug interactions using administrative claims data.

Our work suggests that the ease of implementation of this machine learning approach and its superior results makes it an excellent tool for pharmacoepidemiological analyses of large administrative health databases. The downside of it is that, as with other machine learning

methods, the “black box” approach makes interpretation difficult. While this method can be used to identify those individuals at highest risk of exposure to a high-priority drug-drug interaction, it does not contribute any information of which variables are most important in these predictions. For this purpose, we used a variable importance measurement, and found that the variables related to continuity of care, especially pharmacy and prescriber continuity, were most important in predicting risk of incident exposures to drug-drug interactions.

Continuity of care is associated with better patient outcomes, including better adherence, decreased hospital use, and lower overall mortality.[163] Better continuity of care is associated with lower rates of exposure to drug-drug interactions.[9] Pharmacists play an important role in ensuring continuity of care, especially during care transitions. [164]

Numerous indices measuring continuity of care have been proposed.[165] Geroldinger et al (2018) proposed that separating continuity of care by provider type is a more accurate method of measuring continuity of care. According to their study, including all medical visits with specialists and family physicians or general practitioners within an overall continuity of care index may lead to apparently low continuity of care in a context of high continuity of care among diverse specialists. [92]

Quebec’s healthcare system is based on primary care, with family physicians responsible for referrals to specialist care. If the medical specialties are not considered separately from the family physicians, higher continuity of care may indicate poor access to specialist care. It is thus important to separate the continuity of care indicators according to provider type. The identification of the prescribing physician included in all claims allowed us to compute the continuity of prescriber care, with the idea that even in a context of low continuity of family doctor care, those cases with high prescriber continuity may lead to better outcomes than lower prescriber continuity.

In Quebec, pharmacists are legally responsible for monitoring drug therapies. [64] It is therefore expected that they play a role in preventing exposure to drug-drug interactions, as our results show.

7.1.4 Objective 4: using administrative claims data to assess the association between exposure to drug-drug interactions and adverse events.

The fourth objective was to assess the association between exposure to one of four drug-drug interactions and an adverse event, operationalized as any visit to the emergency department, urgent or semi-urgent hospitalization, or deaths (Chapter 6, Manuscript 3). The drug-drug interactions selected for this outcome were chosen based on their prevalence and expected severity. Three of the four included drug-drug interactions involved the inhibition by proton pump inhibitors of the metabolism of a drug with known or conditional risk for inducing torsades de pointe: citalopram/escitalopram, domperidone, and quetiapine. The fourth drug-drug interaction also involves a drug known to induce torsades de pointe, ciprofloxacin, but whose metabolism was not expected to be affected.

The analysis using current use time-varying drug exposures with Cox proportional hazards regression revealed that exposure to the drug combination of proton pump inhibitors with citalopram was associated with an increased hazard for a visit to the emergency department, hospitalization, or death (HR 1.66, 95%CI 1.36 -2.01 per added combined defined daily dose of drug per day of co-exposure). In the absence of any proton pump inhibitors, each one-unit increase in defined daily dose of citalopram/escitalopram was not associated with an increased hazard for the event (HR 0.97 [0.86-1.09]). However, in the presence of any proton pump inhibitors, the hazard ratios associated with a one-unit increase in citalopram or escitalopram are 1.19 (1.06-

1.35), 1.47 (1.22-1.77), and 2.22 (1.55-3.18) for PPI DDD values of 0.5, 1, and 2, respectively. This suggests that the predicted drug-drug interaction between citalopram/escitalopram and proton pump inhibitors leads to increased hazard for an adverse event. This was not observable in the effects considering cumulative dose of the past 7 and past 30 days. There was evidence of a multiplicative interaction, with the relative excess risk due to interaction (RERI) of 1.38 (95% CI: 1.32 – 1.44).

Regarding the drug-drug interaction between proton pump inhibitors and domperidone, via the inhibition of CYP 3A4, I found that co-exposure to a proton pump inhibitor and domperidone on the same day led to a hazard ratio of 1.76 (95% CI 1.21 – 2.56) per day for each increase of one unit in the product of the drugs' doses. In the absence of any PPI, each one-unit increase in defined daily dose of domperidone was not associated with an increased hazard for the event (HR 0.806 [0.539-1.206]). In the presence of any PPI, the hazard ratios associated with a one-unit increase in domperidone were 1.07 (0.77-1.49), 1.42 (0.99-2.04), and 2.50 (1.35-4.62) for PPI DDD values of 0.5, 1, and 2, respectively. Using the current use model, I found evidence for a multiplicative interaction in the association between the exposure to proton pump inhibitors and domperidone and daily hazard of an adverse event (multiplicative relative excess risk due to interaction of 1.61, 95% CI: 1.51 – 1.71). Co-exposure to PPI and quetiapine was not associated with an increase in the hazard ratio above what could be expected from the combination of both drugs, i.e., there was no evidence of a statistical multiplicative interaction (current use HR 1.09, 95% CI: 0.66 – 1.78, RERI = 0.96, 95% CI: 0.89 – 1.04).

The final drug combination investigated involved proton pump inhibitors with ciprofloxacin. The current use model revealed a marginal hazard ratio of 1.40 (1.03 – 1.77) per day of exposure for each one-unit increase in the product of the defined daily doses of both drugs. In the absence of

any proton pump inhibitor, an increase in of defined daily dose of ciprofloxacin was associated with a hazard ratio for the event of 2.80 (95% CI 2.30 – 3.39). In the presence of PPI on the same day, the hazard ratios associated with a one unit increase in the defined daily dose of ciprofloxacin were 3.30 (2.63 – 4.14), 3.90 (2.71 – 5.62), and 5.45 (2.68 – 11.05) for PPI doses of 0.5, 1, and 2, respectively. The presence of a multiplicative interaction was confirmed with a RERI of 1.26 (95% CI: 1.09 – 1.47).

These results collectively suggest that the drug-drug interactions caused by exposure to proton pump inhibitors and citalopram/escitalopram, domperidone, and ciprofloxacin are associated with an increased risk for a visit to the emergency, a hospitalization, or death.

The use of pharmacoepidemiologic methods with observational data is a necessity in the study of the clinical consequences of exposure to drug-drug interactions, as the sample sizes needed to detect clinical outcomes are too large for a trial. [166] Other studies using real-world data to assess the impact of drug-drug interactions have been conducted. A study using a random sample of the full population included in the national administrative health databases from the compulsory national health insurance program in Taiwan (2000- 2013) found that cumulative exposure to citalopram and proton pump inhibitors was associated with an increased hazard for a sudden cardiac arrest.[136] A recent study found that the combination of citalopram/escitalopram with proton pump inhibitors was associated with sudden cardiac death among people living with end-stage renal disease and receiving hemodialysis. This study used the US Renal Data System, which contains a combination of linked administrative data and electronic health records, and included adults aged 18 or older living with end-stage renal disease. [167]

Studies of the clinical impact of exposure to pharmacodynamic drug-drug interactions between drugs with a known risk for torsades de pointe among have also been conducted. These found that

not all pairwise combinations of drugs with known risk of torsades de pointe lead to increased risk of ventricular arrhythmia [168] or corrected QT prolongation.[169] These studies were conducted on adults aged 65 years or older, and counted any pairwise combinations of drugs with known or conditional risk for torsades de pointe without regard to the potential for pharmacokinetic drug-drug interactions leading to increased exposure (i.e., higher maximum plasma concentration for longer time). In contrast, our study considered combinations of drugs with known or conditional risk of causing torsades de pointe and with a predicted clinically relevant drug-drug interactions due to inhibition of specific cytochrome P450 enzymes. One of these studies used German pharmaceutical claims data.[168]

Drug-drug interactions represent a known preventable source of patient harm and subsequent health system burden. To our knowledge, this work is the first to assess the frequency of exposure to, and the risk of harm from, exposure to drug-drug interactions among community-dwelling non-elderly using administrative health data in Quebec and Canada. Further work on this topic is needed in the Canadian context, especially as the Canadian healthcare systems struggle with COVID-19-related staffing and capacity shortages. Preventing harm from drug-drug interactions may help ease the burden by preventing hospitalizations: a study in Vancouver in 2005 found that 2.9% of hospitalizations over a four-month period were due do drug-drug interactions.[170] A more recent study in the U.S. found that 6.9% of those exposed to drug-drug interactions were found to develop an adverse event of significant to fatal severity.[66] The same annual rate in Canada would mean that over the course of the study, 186 out of 2695 individuals with incident exposure to at least one drug-drug interaction in Manuscript 2 faced a significant to fatal adverse event (N=56,661 individuals at risk for an incident exposure to at least one drug-drug interaction),

assuming that only incident exposures to a drug-drug interaction can lead to an adverse event. While this may seem like a small proportion of those exposed to drug-drug interactions, the large volumes of prescription and numbers of people exposed to multiple drugs renders this a significant problem: a recent study in an English hospital found that 5.4% of hospitalizations over a one-month period were due to drug-drug interactions (29.4% of adverse drug events, which were the cause of 16.5% of all hospitalizations).[29] In Canada in 2020-2021, 2.4% of hospital admissions were due to acute myocardial infarctions, and 1.8% due to COVID-19,[171] potentially placing drug-drug interactions as a higher-ranked cause of admission than these two conditions combined. Thus, efforts to proactively identify and prevent harmful drug-drug interactions need to be fostered.

7.2 Implications for policy

Prescription drugs represent the most widely used and important tool of modern medicine. With expenses on prescription drug among the top drivers of healthcare spending around the world, and adverse drug events as a leading cause of severe harm and death, the implementation of strategies to improve drug safety is an urgent need to ensure the sustainability of our healthcare systems worldwide. As a major cause of preventable adverse drug events, drug-drug interactions should be prioritized.

Regarding manuscript 1, the findings of our systematic literature review and meta-analysis revealed that there is wide variability in exposure to drug-drug interactions across health systems and study settings. The more recent population-wide studies included in our review revealed that exposure to drug-drug interactions is highly prevalent among community-dwelling non-elderly

adults. [145, 151, 157, 158], and there is a trend for increased prevalence of exposure to polypharmacy and drug-drug interactions over time.[145, 157, 172] This means that studies on the prevalence and impact of exposure to drug-drug interactions need to be kept up to date to reflect current drug exposure patterns.

We did not find any studies conducted in Quebec or Canada measuring exposure to drug-drug interactions among adult outpatients. While studies from other countries are informative, Canada faces a unique set of circumstances; for example the Canadian consumption of prescription drugs is higher by volume than the OECD average,[159] and Canadians struggle to access healthcare in a timely manner.[173] The scarcity of information on this important topic signals an urgent need for more research in the Canadian context.

In addition, our systematic review revealed a lack of consistency in the methods used to assess and report the prevalence and rate of exposure to drug-drug interactions across studies. This is an issue that must be addressed to generate a better understanding of the health burden posed by exposure to drug-drug interactions in Canada and around the world. Methodological rigor and reporting transparency, as encouraged by the EQUATOR (Enhancing the Quality and Transparency of health Research) network, can help in this regard.[174] Furthermore, the use of a standardized source of high-priority drug-drug interactions would help drug-drug interaction researchers and regulators to compare exposure rates across studies and populations. [14, 175]

The creation of an open-sourced list of clinically-relevant drug-drug interactions based on the list of high-priority drug-drug interactions created by the Office of the National Coordinator for Health in the U.S.[112] using the AZCERT QT drug list[74] and DrugBank[113] allowed us to conduct a transparent analysis of the frequency of exposure to drug-drug interactions in Quebec. The methods to create this list with updated resources are available in Appendix 2.

With respect to manuscript 2, we found that 11.7% of non-elderly community-dwelling adults were exposed to at least one high-priority drug-drug interaction during 12 months in 2015-2016. This large proportion of exposure warrants further investigation into the health effects of this exposure. Canadian federal and provincial regulators with access to administrative claims data should consider the monitoring of the prevalence of exposure to harmful drug-drug interactions. Furthermore, clinicians should be aware that Quebec non-elderly adults are highly exposed to high-priority drug-drug interactions and consider this exposure as a potential cause of a health emergency.

Most prescriptions in our cohort were issued by family physicians, consistent with reports from the United States [30] and the United Kingdom[31], highlighting the importance of prioritizing the promotion of safe medication use in primary care, as recommended by the World Health Organization. [3]

The finding that lower continuity of pharmacy, pharmacist, and prescriber care were among the most important predictors of the risk of exposure to a drug-drug interaction suggests that strategies fostering the continuity of care around drug prescribing and dispensation may help in the prevention and monitoring of drug-drug interactions. While strategies such as encouraging greater use of drug electronic health records shared across providers may help maintain informational continuity, the relational aspects of continuity of care may also play a role. For example, a stronger provider-patient therapeutic relationship may lead to improved communication and has been associated with improved adherence to medications. [176] Fostering pharmacy loyalty may thus be a useful strategy to prevent exposure to drug-drug interactions. Drug reconciliation efforts in primary care should include all patients, not only those traditionally considered at risk of exposure to drug-drug interactions.

Regarding manuscript 3, the methods presented in this thesis can be used to generate signals of harm from exposure to drug-drug interactions for subsequent investigation. The routine calculation of dose-specific hazard ratios for common drug-drug interactions may be a useful tool to guide clinicians make prescribing decisions. Furthermore, it may help in the identification of especially harmful drug-drug interactions among the population of Quebec.

The information obtained from analyses of the impact of exposure to drug-drug interactions can be used as the first step towards more in-depth investigations of the effects of specific drug-drug interactions. Currently, post-marketing surveillance is based on spontaneous adverse event reports, and predicted drug-drug interaction information is extrapolated from *in vitro* results. [166] While spontaneous adverse event reporting systems represent an invaluable source of information, they are also limited to those incidents occurring to patients with clinicians who correctly and confidently identify the drug-drug interaction and who are willing to expend the time and effort into filing a suspected adverse event report. In practice, it is estimated that less than 5% of adverse drug events are reported to spontaneous reporting systems.[55, 177] Furthermore, clinicians often fail to recognize drug-induced adverse drug events,[27] and arguably drug-drug interactions are even more complicated to identify because the number of possible pair-wise combinations of existing drugs is so large. [166] An improvement of the quality of the knowledge used to classify drug-drug interactions as clinically-relevant is needed to prevent a potentially leading cause of hospitalization. [29] The approach proposed in this thesis of using administrative health data to routinely measure the frequency and impact of exposure to drug-drug interactions could complement these current sources of information with a systematic approach. This type of drug-exposure based assessment is considered a type of active pharmacosurveillance.[178]

The active surveillance of the consequences of exposures to harmful drug-drug interactions needs to be undertaken. For example, in 2014 the Canadian Institute for safe medication practices (ISMP) issued a warning in 2014 against combining the antidepressant citalopram and the antibiotic azithromycin, describing a case of preventable death due to this DDI. [179] However, we identified 113 individuals in our cohort with a combined 571 days of exposure to this DDI in 2015-2016 for whom the consequences remain unknown. The establishment of high-priority drug-drug interactions and active surveillance[178] of these exposures could greatly help advance patient safety in Quebec and Canada.

In Quebec, the National Institute for Excellence in Health and Social Services (INESSS) is a provincial public institution with the mission of promoting the best possible care in Quebec at the lowest possible cost. In addition to responding to ministerial inquiries, INESSS is mandated with monitoring the optimal use of medications in Quebec and has access to all the provincial administrative health databases to do so. INESSS produces a variety of knowledge products, including drug optimal use guides, which are disseminated to clinicians in the province.[180] As such, INESSS is perfectly positioned to implement a system to monitor the optimal use of drugs in Quebec, including the prevalence and impact of exposure to drug-drug interactions, and disseminate the findings across the province.

This thesis has demonstrated the utility of Quebec's administrative health databases to measure the frequency of exposure to drug-drug interactions among community-dwelling adults. INESSS demonstrated strategic vision by integrating the assessment of the frequency and impact of exposure to drug-drug interactions within their annual triennial plan (2019-2022).[181] Hopefully this type of work can continue and can find the contributions of this thesis useful. For example, the list of high-priority drug-drug interactions, the SAS codes and tables needed to convert drug

claims to active ingredients, and the SAS and R codes to model time-varying drug exposure were provided to INESSS as a deliverable from this work in the hopes that these will facilitate the replication of these analyses with any population and drugs of interest. There is thus a potential for this work to directly help the analysts providing evidence to guide policy and clinical practice. As mentioned above and in the background, INESSS occupies a central role in guiding both policy and clinical decisions in Quebec.

Other countries have their own databases of clinically relevant drug-drug interactions. For example. the Finnish Ministry of Health and Social Affairs and the Swedish Stockholm County Council and Karolinska Institute collaborated in the creation of a comprehensive drug-drug interaction database for inclusion in clinical decision-support systems, the Swedish-Finish interaction X-referencing knowledge base (SFINX).[182] SFINX was integrated into Finnish clinical decision support systems in 2005 and into Swedish clinical decision support systems in 2007. [183] Its inclusion in computerised clinical decision support systems in Sweden led to a modest reduction in the prevalence of exposure to the highest severity drug-drug interactions (type D).[183]

Beyond the specific investigation of drug-drug interactions, health agencies tasked with assessing the optimal use of medication and medication safety need to integrate an analysis of the prevalence and impact of exposure to drug-drug interactions when analyzing the safety profile of individual drugs. Single drug safety analyses fall short of what is required by our modern use of drugs. Our results found that many highly prevalent drugs were found in co-exposure with other drugs more often than alone. Thus, ignoring the effect of co-exposures and potential drug-drug interactions within those co-exposures may miss an important source of patient harm.

In 2014, a law entitled Vanessa's Law: Protecting Canadians from Unsafe Drugs came into effect in Canada.[62] This law makes the reporting of serious adverse drug reactions mandatory for hospitals, gives Health Canada the power to recall approved drugs, and gives the Canadian Health minister the power to order the pharmaceutical company who owns a therapeutic license to conduct further studies on the safety of their product and to report the results of their findings to the minister. However, research has shown that most adverse events due to drugs are either not identified or not reported.[27, 55] Thus, active surveillance may be needed to enhance patient safety from unsafe drug exposures.

7.3 Limitations

This thesis is not without limitations. The systematic literature review and meta-analysis was limited by the information presented in the included studies. The small number of studies eligible for meta-analysis was too small to conduct a meta regression to assess the impact of study methods such as the data sources and the definitions of drug-drug interaction used.

The sources of data used for Manuscripts 2 and 3 were administrative health databases created and maintained for billing purposes. As such, they lack medical details which could be of key importance for addressing confounding in these studies. As with other pharmacoepidemiological studies, there is likely to be considerable confounding by indication. The use of a causal framework to control for this would greatly enhance the usefulness of these results. Whether this is feasible using only administrative health databases remains to be seen.

Regarding the assessment of drug exposure, I assumed that individuals were exposed to drugs starting on the date of first purchase and for the duration indicated on the claim. However, some inaccuracies may be introduced for medications used "as needed". A study by Blais and colleagues

found that there is poor agreement in the days' supply for asthma inhalable medication among children living with asthma and actual exposure to these medications.[184] We may thus be overestimating the prevalence and incidence of exposure to drug-drug interactions.

Another source of overestimation of the exposure to drug-drug interactions may be due to the timing of the exposure required to trigger a clinically relevant effect. In this study, a person was considered exposed to a drug-drug interaction if there was an overlap between two interacting drugs of at least one day. Some drug-drug interactions may require longer exposure times or specific timing to lead to an adverse drug event.

Furthermore, no over-the-counter medications were included in this work, as these are not covered by the public drug insurance and as such do not appear in the claims database used in Manuscripts 2 and 3. Individuals choosing to forgo public coverage to pay out of pocket for a drug (e.g., for a brand name drug not covered by the public plan) would have missing data for the drug paid out of pocket. Similarly, drugs administered during hospital stays were not included in any of the analyses.

The effect of these exposure misclassifications would be to bias the effect estimates towards a null effect in our study of the association between exposure to drug-drug interactions and adverse events, underestimating their magnitude. Despite these limitations, prescription claims such as those contained in administrative health data are more representative of actual consumption patterns than electronic medical records, as they require the patient actively seeking the medications and not all prescribed drugs are purchased by patients. [185, 186]

The cohort studied in Manuscripts 2 and 3 was comprised of individuals with continuous coverage under the public prescription drug insurance program of Quebec. This includes self-employed

individuals without access to private insurance through an employer, and those receiving financial assistance, leading to an over representation of individuals with higher index of social and material deprivation and limiting the generalizability of our results to the overall population of non-elderly community-dwelling adults in Quebec. Importantly, these data do not include any Indigenous people who are beneficiaries of the James Bay and Northern Quebec Agreement (Cree and Inuit) or the Northeastern Quebec Agreement (Naskapi), nor First Nations and Inuit people registered with Indigenous Services Canada. [110] This situation leads to a gap in knowledge specifically concerning certain groups of indigenous people in Quebec.

For the final objective of assessing the impact of exposure to drug-drug interactions, the analysis included a composite outcome including all deaths, hospitalizations, and visits to the emergency department. No attempt was made to use diagnostic codes to identify potential adverse drug events. While the initial plan was to conduct separate analyses for each outcome, resource constraints resulting from the stress placed on Quebec's healthcare system as a result of the COVID-19 pandemic precluded the creation of a sufficiently large sample of individuals to conduct outcome-specific models. The use of the data for the full population of adults in Quebec in this analysis would allow for a more detailed analysis, including separate analyses for each outcome, and the use of diagnostic codes to identify specific outcomes.

The choice of study duration may impact the magnitude of the hazard ratios obtained using Cox proportional hazard models, as the obtained hazard ratio is averaged over the duration of follow up. [187] Similarly, as the population at any given day is composed only of those individuals who have not yet experienced an outcome, the hazard ratio on that day has a selection bias; individuals susceptible to the outcome will gradually be depleted with increasing duration of follow-up. No analyses with shorter durations of follow-up were conducted in this study.

7.4 Future work

Few studies have been conducted assessing adverse events due to drugs among community-dwelling patients. [188] More studies investigating the frequency and impact of exposure among community-dwelling non-elderly adults in Canada are needed to fill this knowledge gap. To be able to compare results from such studies, consistent methods should be followed; a reporting guideline for studies assessing drug-drug interactions may also be a worthy project that helps drug-drug interaction researchers.

While the prevalence of exposure to drug-drug interactions may be high, it is likely that even the most harmful DDI may lead to harm in a minority of patients. Thus, the challenge of further refining and identifying subpopulations for whom each drug-drug interaction is relevant is key to assist regulators and clinicians in conducting harm to benefit assessments. Population-wide studies with outcome-specific analyses conducted routinely by regulators with access to relevant data may be the first step to identify such subpopulations. Similarly, the use of a causal framework when measuring the association between exposure to drug-drug interactions and adverse events can provide confounding control lacking in this study.

As mentioned before, the databases used in this thesis do not include Quebec residents who are insured under an indigenous-peoples statute or program. Thus, investigations into the exposure and impact of drug-drug interactions among Indigenous people of Quebec need to be conducted.

CHAPTER 8: CONCLUSION

Our synthesis of the scientific literature found that 18 % (95% CI 9% - 35%, 95% PI 1% - 80%) of non-elderly adult outpatients exposed to two or more drugs are exposed to predicted drug-drug interactions (wide prediction intervals). Our empirical results measuring the exposure to drug-drug interactions in Quebec found that 19% (95% CI: 18.7% – 19.5%) in this population with two or more drug claims were exposed to prevalent drug-drug interactions over 12 months in 2015-2016. This finding is close to the pooled prevalence of 18% found in our meta-analysis. A total of 850 different drug-drug interactions were identified in 30,385 episodes of exposure to drug-drug interactions, with a median duration of 15 days each (IQR 5, range 1 to 365 days). The majority of drug-drug interactions identified involved two drugs with a known or conditional risk of leading to the potentially deadly long QT syndrome. Using ensemble machine learning approach SuperLearner, we found that the number of different drugs claimed, the continuity of pharmacy and pharmacist care, and the continuity of prescriber care were important variables at predicting subsequent incident exposure to drug-drug interactions over 12 months. Finally, our study of the impact of exposure to select drug-drug interactions found that exposure to three out of four drug-drug interactions investigated (proton pump inhibitors in combination with either of citalopram/escitalopram, domperidone, or ciprofloxacin) was associated with increased daily hazards for experiencing an adverse event (visit to the emergency department, hospitalization, or death).

Our systematic review and meta-analysis confirmed that the population of community-dwelling non-elderly adults is underrepresented in studies about drug-drug interactions, and no Canadian studies measuring drug-drug interactions in this population were found. Thus, we sought to measure this prevalence in our home province of Quebec, using administrative health databases,

and found the expected high prevalence and incidence of exposure to drug-drug interactions. We found that Quebecers were highly exposed to drug-drug interactions and sought to assess whether this exposure was associated to patient harm. We then used dose-specific daily drug exposures to measure the association between selected drug-drug interactions and the risk of an adverse event.

In conclusion, this work provides evidence that exposure to drug-drug interactions is highly prevalent among community-dwelling non-elderly adults around the world and in Quebec. Encouraging moderation when prescribing, and increased continuity of prescriber, pharmacy and pharmacist care may help prevent exposure to drug-drug interactions in this population. Finally, administrative health databases can be used to identify drug-drug interactions associated with increased hazard for an adverse event. Further work is needed to validate the findings presented in this thesis.

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APPENDIX 1: DATA EXTRACTED TO STUDY DRUG-DRUG INTERACTIONS IN QUEBEC

A cohort of containing a 5% random sample of the database population of the public drug insurance of Quebec with continuous coverage between April 1, 2014 and March 31, 2017 was extracted from the RAMQ databases by the data management team of the National Institute for Excellence in Health and Social Services (INESSS). Using an anonymized identifier to link across databases, health service use data for the individuals in the cohort was extracted from the RAMQ and MSSS databases, as described in the table below.

This data was used to address objectives 2, 3 and 4 in this thesis; the first year (April 1, 2014 to March 31, 2015) was used to measure baseline characteristics. The 12-month prevalence and incidence of exposure to drug-drug interactions was measured between April 1, 2015 and March 31, 2017 (objectives 2 and 3). The association between exposure to drug-drug interactions and adverse events was measured over 24 months between April 1, 2015 and March 31, 2017.

Data Source	Variables	Description
Fichier d'inscription des personnes assures (FIPA)	Sex, date of birth, date of death, index of material deprivation	A 5% random sample of the database population aged 18 to 63 years on April 1, 2014 N = 63,834 Individuals residing in long term care were excluded from the cohort on the basis of their eligibility for the public drug insurance.
SMED (Drug claims)	Type of coverage plan, date of claim, duration of prescription, drug code, amount of medication dispensed, dosage, form, prescriber ID, specialty of prescriber, dispensing pharmacist ID, pharmacy establishment	All claims linked to the cohort were extracted. 67% of the cohort had at least one claim in the 3 years between April 1, 2014, and March 31, 2017. N = 6,724,888 claims Excluded: Claims relating to non-drug materials (syringes, etc) were excluded by their *Code de forme*: pansement (5548, 5679), trousse (3103), bandelette (3828), seringue (5613), bandage (58), lamelle (3248), poudre usage externe (5678).

		Non-dispensing services provided by the pharmacy were excluded on the basis of the service codes present in the claim: transmission of patient profile, pharmaceutical opinion, consultation, emergency transport, packaging fees.
SMOD (Medical acts billed by the act)	Date of the act, provider's specialty, ICD-9 diagnostic code, category of establishment where act took place	All medical acts dated within the 3-year period between April 1, 2014, and March 31, 2017 linked to individuals in the cohort were extracted. N = 1,804,557 medical acts were identified, involving 58,539 individuals (92% of the cohort).
Enrolment with family physician (Fichier GMF)	Category of relationship, start date, end date, class of provider	The list of enrolment with family physicians was extracted for every member of the cohort.
Hospitalizations (MED-ECHO)	Date of admission, date of departure, date of registration in emergency room, admission diagnostic, main diagnostic, type of care, type of admission	All hospitalization episodes for individuals in the cohort during the 3-year period from April 1, 2014 to March 31, 2017 were extracted. N = 24,313 hospitalization episodes involving 12 623 individuals (20% of the cohort population)

BDCA (Emergency department use)	Date of arrival at ED, date of departure from ED	All visits to the emergency department during the the 3-year period from April 1, 2014 to March 31, 2017 were extracted. N = 65,985 visits to the emergency department were identified involving 13,905 individuals (22% of the cohort population)

APPENDIX 2: CREATION OF AN OPEN-SOURCE LIST OF HIGH-PRIORITY DRUG-DRUG INTERACTIONS

Sources:

1. High-priority DDI from the ONC

The ONC list of the U.S. Office of the National Coordinator for Health Information Technology led a project to identify high-priority drug combinations, expected to lead to clinically important DDI. A consensus-based process produced a list of fifteen drug class – drug class combinations expected to lead to clinically important effects. In addition to specific DDI between drug pairs, this list included combinations between QT prolonging agents as classified by CredibleMeds.org (formerly torsades.org).

2. List of drugs with known or conditional risk of leading to torsades de pointe from Credible Meds

A list of all drugs with known, possible, or conditional risk of leading to long QT and torsades de pointe is curated by Credible Meds (AZCERT) and can be downloaded from their website.

3. Validation of DDI between QT drugs using DrugBank

DrugBank is an open resource containing vast amounts of information on every drug, including all empirically determined DDI. The DrugBank team manually searches literature and curates this list, which can be accessed as a downloadable XML document.

4. Combinations of opioids and benzodiazepines

The increased use in prescription opioids seen in recent years has led to many deaths due to opioid overdoses. Several studies have flagged increased co-prescribing of these two drug classes, and increased rates of fatal overdoses.[1, 2]

Methods:

A list of drug-drug interactions based on the ONC list was created. When the suggested DDI involved specific drug combinations, these were included directly. For example, the DDI between

amphetamine derivatives and MAO inhibitors specifies that the combination of dexmethyphenidate (an amphetamine derivative) and tranylcypromine (a MAO inhibitor) should be considered a high-priority DDI. When no specific drugs were identified (e.g., the DDI between tricyclic antidepressants and five MAO inhibitors does not identify any specific tricyclic antidepressant), the approved drugs belonging to this class were identified using the online resource RxTx, compiled by the Canadian Pharmacists Association.

The ONC list of high-priority DDI includes the combination of two QT-prolonging drugs as a high-priority DDI. However, recent studies have shown that not all combinations of QT-prolonging drugs lead to an increased risk of long QT and lethal arrhythmias beyond what could be expected from both drugs.

DrugBank (version 5.1.4) was downloaded from the website as an XML file. A data frame containing the list of all DrugBank DDI was created using R package "XML2".

A list of all drugs with known or conditional risk of leading to long QT and torsades de pointe (hereafter, QT drugs) was downloaded from CredibleMeds.org on July 19, 2019. All QT drugs obtained from Credible Meds were assessed for the presence of potential pharmacokinetic or pharmacodynamic DDI with other QT drugs using DrugBank.

A list of opioids and benzodiazepines in regular use among adult outpatients was obtained from RxTx. All possible combinations of active ingredients in these categories was created, and validated through the use of DrugBank to identify opioid-benzodiazepines pairs which are known to lead to a pharmacodynamic or pharmacokinetic DDI.

The full list of DDI can be found at https://github.com/DDI-QC/DDI-list

APPENDIX 3: COUNTING OUTPATIENT MEDICAL VISITS

The number of outpatient medical visits with all doctors and with family physicians during the baseline period were counted for each patient.

Medical billing data is generated for each medical act performed by a healthcare provider for a service covered by the public insurance.

In Quebec, multiple acts can be performed and billed within a single medical visit. We counted as a single medical visit all acts billed by a physician for the same patient on the same day. Only acts performed by a physician were retained. Any medical act billed within an episode of hospitalization, as identified from the MED-ECHO database, was excluded. Acts taking place in the emergency department outside of hospitalization episodes were included.

APPENDIX 4: DATA CLEANING PRODUCTS PRODUCED AT INESSS DURING THIS THESIS

Conversion of RAMQ DC drug codes to unique active ingredient codes

Contexte et problématique: les médicaments sont une partie intégrale des ressources thérapeutiques dans le secteur de la santé. L'évaluation de l'utilisation des médicaments par les Québécois(es) requiert une préparation des données brutes contenues dans les banques de données médico-administratifs de la Régie de l'assurance médicament.

Chaque médicament est assigné plusieurs codes à des fins diverses, tels que les codes DIN, ATC, AHFS, et les codes de dénomination commune identifiant chaque ingrédient actif ou médicinal. Ces codes de dénomination commune sont associés aux noms génériques des médicaments, indépendamment de la marque commerciale, teneur, ou forme pharmaceutique. Certaines évaluations de l'utilisation des médicaments requièrent l'évaluation de l'utilisation des médicaments par ingrédient actif, tels que les évaluations sur l'usage et efficacité et sécurité des médicaments.

La plupart des codes DC dans la banque de données de produits pharmaceutiques (SMED) correspondent à des ingrédients actifs ou médicinales, mais regroupent aussi parfois plusieurs ingrédients actifs dans le même code; parfois, il existent des codes DC pour les ingrédients non-médicinales, comme les syringes.

Les codes DCQC ont été créés par l'ancien bureau de la Gestion de l'information de l'INESSS, pour faciliter l'analyse de données correspondant à un sous ensemble de codes DC correspondant à des médicaments consommés par un échantillon d'adultes âgés de 65 ans et plus.

Objectifs :

Fournir un tableau de conversion entre les codes DC de la RGAM et les codes DCQC de l'INESSS pour la totalité des codes de dénomination commune remboursées par la RGAM entre les années 2008 et 2018.

Proposer une méthode pour l'actualisation périodique de ces codes.

Méthodes :

1. Identification des codes DC comprenant plusieurs ingrédients actifs

Si le code DC regroupe plusieurs ingrédients actifs, il est séparé dans le nombre d'ingrédients actifs contenus. Chaque ingrédient actif est désigné par son propre code DCQC.

Chaque code DC est associé à un nom de dénomination commune. Les noms des codes DC portant plusieurs ingrédients actifs incluent au moins un des symboles «/», « , », ou «-» pour séparer le nom de chaque ingrédient actif. Une recherche textuelle pour ce caractère peut être utilisé pour identifier les codes DC associés à plusieurs ingrédients actifs et ceux associés à un seul ingrédient actif.

1.1 Séparation à des codes pour chaque ingrédient actif

Les charactères de séparation « / », « , », et « - » peuvent être utilisés pour indiquer le point de séparation des ingrédients actifs et la création d'une nouvelle colonne contenant une sous-chaine du nom originale. Une transposition des nouveaux noms permet de créer une nouvelle ligne de données pour chaque ingrédient actif.

1.2. Assignation de codes DCQC pour chaque ingrédient actif

La liste de codes DC associés à un seul ingrédient actif est recherchée pour chaque ingrédient actif séparé, et le code DCQC attribué à chaque ingrédient actif est identique au code DC déjà existant.

Dans les cas des codes DC à multiples ingrédients actifs qui n'ont pas un DC existant, un nouveau code DCQC est attribué avec la formule 100000 + (code DC originale à multiples ingrédients actifs). Dans le cas où il existe plus d'un ingrédient actif sans code DC existant, on continue à attribuer des nouveaux codes utilisant 200000 + (code DC originale) pour le deuxième ingrédient actif.

2. Dédoublement des codes DC différents pour le même ingrédient actif

Les codes DC associés à un seul ingrédient actif sont triés par nom de dénomination commune (nom DC) et les doublons sont identifiés. Si plus d'un code existe pour le même ingrédient actif

(par. ex., pour un sel différent du même ingrédient actif), le code DCQC est le premier code DC désignant cet ingrédient actif.

La même procédure est suivie pour les fournitures et produits ne contenant pas des ingrédients médicinaux actifs.

Résultats

Mille onze (1011) codes DCQC ont été créés à partir de 1271 codes DC.

Un totale de 1085/1271 codes DC étaient associés à un seul ingrédient actif, 156/1271 à deux ingrédients actifs, 20 à trois, huit à quatre, un à cinq et un à six.

Le tableau de conversion est fourni en format csv.

Conclusion

La conversion des codes DC a des ingrédients actifs est un effort qui permet l'analyse de l'utilisation des médicaments par ingrédient actif.

Classification des codes DCQC

Contexte et problématique:

Les codes DCQC ont été préparés de façon qu'un code correspond à un ingrédient. Parmi tous les ingrédients actifs médicinaux, ils existent des codes DCQC correspondant à des ingrédients qui ne sont pas des ingrédients actifs thérapeutiques (drogues). Il est utile d'identifier ces éléments pour faciliter les analyses des données sur l'utilisation des médicaments.

Les produits pharmaceutiques classiques comportent la majorité des ingrédients actifs thérapeutiques; ils sont les médicaments à petites molécules, aussi connus comme drogues.

Les produits biologiques sont des produits utilisés pour la prévention ou traitement des maladies humaines, et qui sont dérivés du tissu vivant, soit animale, humaine, ou des microorganismes. Les produits biologiques ont généralement une structure très complexe, et ne sont pas bien caractérisés.[3-5]

Méthodes

Une classification dans cinq catégories a été faite :

1. Produits pharmaceutiques classiques (petites molécules, ou drogues)
2. Produits biologiques
3. Vitamines, minéraux et suppléments nutritifs
4. Excipients, réactifs, diluants, eau
5. Matériaux d'administration

Produits pharmaceutiques classiques

Cette catégorie regroupe la majorité des produits trouvés dans la banque de données de la RGAM. La classification dans cette catégorie à été faite par élimination et par inspection visuelle. Tous les produits non classifiés dans les catégories 2 à 5 ont été inspectés pour assurer leur classement dans la catégorié indiquée.

Produits biologiques

L'identification des produits biologiques a été faite en se basant sur les données de la Base de données des avis de conformité (AC) du Gouvernement du Canada[6]. Les AC sont émis aux fabricants des médicaments si le produit est jugé conforme au Règlement sur les aliments et drogues. Tous les produits pharmaceutiques au Canada ayant eu un AC depuis le 1er janvier 1994 et jusqu'au 29 mars 2018 y sont incluses.

La base de données des AC classifie les produits pharmaceutiques dans les catégories :

- Produits pharmaceutiques sur ordonnance
- Produits pharmaceutiques en vente libre
- Produits biologiques
- Produits radiopharmaceutiques
- Produits vétérinaires

Les produits biologiques ont été identifiés grâce a cette classification de la base de données des AC. Une recherche par mots-clés a aussi été complétée pour identifier comme produits biologiques les produits avec les mots :

- vaccin
- allergène
- hyménoptère
- galactosidase
- toxine

Vitamines, minéraux et suppléments nutritifs

Le Fichier Canadien sur les éléments nutritifs [7] était la référence utilisé pour identifier les produits nutritifs parmi les médicaments. Le tableau contenant les noms de tous les produits nutritifs disponibles au Canada (147 au total) a été téléchargé, modifié, et utilisé pour identifier les vitamines, minéraux, et suppléments nutritifs. Les modifications portées ont enlevé certains mots qui généraient des problèmes (ex., le potassium est un élément nutritif mais aussi présent dans plusieurs noms de médicaments, alors c'est enlevé de la liste).

Excipients, réactifs, diluants, eau

L'identification des produits appartenant à cette catégorie ont été identifiés par une recherche des mots clés suite par une inspection de chaque code identifié.

Les mots-clés recherchés dans cette catégorie sont :

- Goudron
- Huile
- Eau
- Alcool
- Base
- Diluant
- Réactif
- Petrolatum
- Paraffine
- Chloral
- Glycérine
- Polyvinylique

Matériaux d'administration

L'identification des produits appartenant à cette catégorie ont été identifiés par une recherche des mots clés suite par une inspection de chaque code identifié.

Les mots-clés recherchés dans cette catégorie sont :

- Bouchon
- Aiguille
- Seringue
- Cassette
- Chambre
- Vide
- Bandelette
- Pansement

Résultats

Produits pharmaceutiques classiques

Un total de 864 produits ont été classifiés comme produit pharmaceutique classique à petite molécule.

Produits biologiques

Une liste de 451 produits biologiques a été générée à partir de la base de données des AC.

Cette liste et la recherche par mots clés ont été utilisées pour l'identification de 69 produits biologiques parmi les 1011 ingrédients actifs trouvés dans les données 2016-2017. Le tableau est joint comme fichier csv.

Vitamines, minéraux et suppléments nutritifs

Un tableau contenant 147 éléments nutritifs a été généré à partir des données téléchargées du Fichier Canadien sur les éléments nutritifs.

Ce tableau a été utilisé pour l'identification de 44 produits nutritifs parmi les 1011 ingrédients actifs trouvés dans les données extraites de la base de données SMED.

Excipients, réactifs, diluants, eau

Vingt-quatre des produits ont été classifiés dans la catégorie 4.

Matériaux d'administration

Dix produits ont été classifiés dans la catégorie 5.

Type de produit	**Code**	**Nombre trouvé**
Pharmaceutique (petite molécule)	1	864
Biologiques	2	69
Vitamines, minéraux, suppléments nutritifs	3	44

Excipients	4	24
Matériaux d'administration	5	10
TOTAL		1011

Conclusion

L’utilisation des ressources publiques de Santé Canada et des recherches textuels par mots clés a permis la classification des ingrédients actifs dans de catégories pouvant aider dans la préparation et nettoyage des codes des médicaments.

Conversion des codes de teneur des médicaments

Contexte et problématique:

L'évaluation de l'utilisation des médicaments parfois requiert l'évaluation de la teneur des médicaments. Les codes de la régie d'assurance médicament sont parfois difficiles à utiliser dans des évaluations à grande échelle, car ils contiennent des combinaisons de quantités et unités dans le même champ.

Objectifs :

Fournir un tableau de conversion entre les codes de teneur de la RGAM pour la totalité des codes DIN remboursées par la RGAM entre les années 2008 et 2018.

Méthodes :

La banque de données sur les produits pharmaceutiques du Santé Canada à été utilisée pour assigner les nouveaux codes de teneur associés à chaque DIN.

Résultats

Un tableau avec 6219 codes DIN avec les codes de teneur associés à chaque ingrédient actif compris dans chaque DIN a été créé. Ce tableau présent le teneur de chaque ingrédient actif dans deux champs : teneur (montant, par ex., 2), unité du teneur (par ex. mg); dans le cas où une précision de la posologie de l'ingrédient actif, deux champs additionnels décrivent le volume dans lequel se retrouve le teneur : le volume (par ex. 1) et l'unité de volume (par ex. mL).

APPENDIX REFERENCES

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