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Advances in Therapeutic Risk Management through Signal Detection and Risk Minimisation Tool Analyses

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Résumé

Les quatre principales activités de la gestion de risque thérapeutique comportent l'identification, l'évaluation, la minimisation, et la communication du risque. Ce mémoire aborde les problématiques liées à l'identification et à la minimisation du risque par la réalisation de deux études dont les objectifs sont de: 1) Développer et valider un outil de « *data mining* » pour la détection des signaux à partir des banques de données de soins de santé du Québec; 2) Effectuer une revue systématique afin de caractériser les interventions de minimisation de risque (IMR) ayant été implantées.

L'outil de détection de signaux repose sur la méthode analytique du quotient séquentiel de probabilité (MaxSPRT) en utilisant des données de médicaments délivrés et de soins médicaux recueillis dans une cohorte rétrospective de 87 389 personnes âgées vivant à domicile et membres du régime d'assurance maladie du Québec entre les années 2000 et 2009. Quatre associations « médicament-événement indésirable (EI) » connues et deux contrôles « négatifs » ont été utilisés. La revue systématique a été faite à partir d'une revue de la littérature ainsi que des sites web de six principales agences réglementaires. La nature des RMIs ont été décrites et des lacunes de leur implémentation ont été soulevées.

La méthode analytique a mené à la détection de signaux dans l'une des quatre combinaisons médicament-EI. Les principales contributions sont: a) Le premier outil de détection de signaux à partir des banques de données administratives canadiennes; b) Contributions méthodologiques par la prise en compte de l'effet de déplétion des sujets à risque et le contrôle pour l'état de santé du patient. La revue a identifié 119 IMRs dans la littérature et 1,112 IMRs dans les sites web des agences réglementaires. La revue a démontré qu'il existe une augmentation des IMRs depuis l'introduction des guides réglementaires en 2005 mais leur efficacité demeure peu démontrée.

Mots-clés : Gestion du risque thérapeutique, minimisation du risque, pharmacovigilance,

data mining, détection de signaux.

Abstract

The four main components of therapeutic risk management (RM) consist of risk detection (identification), evaluation, minimisation, and communication. This thesis aims at addressing RM methodologies within the two realms of risk detection and risk minimisation, through the conduct of two distinct studies: i) The development and evaluation of a data mining tool to support signal detection using health care claims databases, and ii) A systematic review to characterise risk minimisation interventions (RMIs) implemented so far.

The data mining tool is based on a Maximised Sequential Probability Ratio Test (MaxSPRT), using drug dispensing and medical claims data found in the Quebec health claims databases (RAMQ). It was developed and validated in a cohort of 87,389 community-dwelling elderly aged 66+, randomly sampled from all elderly drug plan members between 2000 and 2009. Four known drug-AE associations and two "negative" controls were used. The systematic review on RMIs is based on a literature search as well as a review of the websites of six main regulatory agencies. Types of RMIs have been summarized and implementation gaps identified.

The data mining tool detected signals in one of four of the known drug-AE associations. Major contributions are: a) The first signal detection data mining tool applied to a Canadian claims database; b) Methodological improvements over published methods by considering the depletion of susceptibles effect and adjusting for overall health status to control for prescription channelling. The review yielded 119 distinct RMIs from the literature and 1,112 from the websites. The review demonstrated that an increase in RMI numbers among websites occurred since the introduction of guidances in 2005, but their effectiveness remains insufficiently examined.

Keywords: Therapeutic risk management, risk minimisation, drug safety,

pharmacovigilance, data mining, signal detection.

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List of acronyms

ADR – Adverse Drug Reaction

AE – Adverse Event

AERS – Adverse Event Reporting System

AFSSApS - Agence française de sécurité sanitaire des produits de santé,

BBW – Black Box Warning

BCPNN - Bayesian Confidence Propagation Neural Network

BTS – Black Triangle Scheme

CDS – Chronic Disease Score

CERT - Center for Education and Research on Therapeutics

CHF – Congestive heart failure

CIOMS - Council for International Organizations of Medical Sciences

CLSC - Centre local de services communautaire

CM – Conseil du médicament

DPA – Disproportionality Analysis

DREAM - Diabetes Reduction Assessment with ramipril and rosiglitazone Medication

EBAM - Empirical Bayes Arithmetic Mean

EBS - Empirical Bayes Screening

EM – Education Material

EMA - European Medicines Agency

EP – Education Program

EU – European Union

FDA – Food and Drug Administration

GP – General Practitioner

GPS - Gamma Poisson Shrinker

HCP – Health Care Professional

HDPS-High-dimensional Propensity Score

HMO - Health Maintenance Organisation

IC – Information Component

ICD – International Classification of Diseases

ICD-CM - International Classification of Diseases Clinical Modification

ID – Incident Density

IRR – Incidence Rate Ratio

MaxSPRT – Maximised Sequential Probability Ratio Test

MGPS - Multi-item Gamma Poisson Shrinker

MHRA - Medicines and Health Care products Regulatory Agency

NSAIDS – Non-steroidal anti-inflammatory drugs

OR - Odds Ratio

PEM- Prescription-Event Monitoring

PREA- Pediatric Research Equity Act

PRR – Proportional Reporting Ratio

PtAC – Patient Alert Card

RAMQ - Régie de l'assurance maladie Québec

RD – Restricted distribution

ROR – Reporting Odds Ratio

RR- Relative Risk

RRR – Relative Reporting Ratio

SAE – Serious Adverse Event

SMR - Standardised Mortality Ratio

SPRT – Sequential Probability Ration Test

SRS – Spontaneous Reporting System

TDM- Therapeutic Drug Monitoring

W – Product Withdrawal

WHO – World Health Organisation

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Biomedical Science Award, and the Université de Montréal through the Scholarship for Exemption from Québec Supplementary School Fees.

Foreword

This thesis by publication (article thesis) was created during my Master's level studies at the Université de Montréal in the Medication and Public Health option, under the supervision of Dr. Yola Moride. The article included in this thesis, of which I am Principal Author, was accepted for publication in the journal "Drug Safety" at the time of the thesis submission. The article was drafted in collaboration with Anne-Marie Cloutier, Camille Craig, Dr. Jacques LeLorier and my Research Director, Dr. Yola Moride. I contributed substantially to this article in terms of the: method development; evaluation and extraction of data from sources; data analysis and interpretation; and drafting of the manuscript itself.

Chapter 1. Thesis Introduction

1.1 Historical perspectives of drug safety surveillance and therapeutic risk management

Between the years of 1956 and 1961, widespread use among pregnant women of the sedative thalidomide, was linked to the congenital malformation of phocomelia (deformed limbs) in almost 10,000 newborn babies world-wide[1,2,3]. These unfortunate cases were observed in 46 different countries, including Germany, England, and the United States. In fact, the "thalidomide tragedy" is the catastrophe that reformed the regulatory drug testing and drug approval processes on a global scale, eventually leading to the emergence of the field of pharmacovigilance, or safety surveillance[4]. Since then, regulatory agencies around the world have implemented surveillance methods, mainly based on spontaneous reporting in order to support timely signal detection, the identification of new AEs[5]. In parallel, pharmacovigilance regulations have been harmonized through the International Conference on Harmonization (ICH) E2E. Although Canada is not formally part of ICH, it is an observer and also follows ICH E2E.

Despite the success of medications at reducing morbidity and increasing life expectancy, drugs can also be associated with adverse events (AEs), some of which are serious, debilitating, and even life-threatening. In 2005, the Cox 2 Inhibitor, rofecoxib, and its reported link to myocardial infarct and stroke resulted in the product's withdrawal from the market, and the subsequent voluntary withdrawal of the entire class of drugs[6]. This subject has been largely debated [7,8], as some wonder what precautions could have been taken in

order to avoid or reduce the occurrence of these AEs, and whether i) limiting the product as a treatment of last resort to be used by those for whom other treatments had not been successful and; ii) more stringent adherence to the labelling instructions by prescribers; may have permitted this product to remain on the market. This would have allowed the continued and much-needed benefit for those individuals for whom rofecoxib was the only effective treatment[7],.

The suggested rofecoxib activities described in points i) and ii) above are examples of possible components of a therapeutic risk management system/plan, i.e. a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of the effectiveness of those interventions. [9]

1.2 Components of therapeutic risk management

Risk management consists of four main activities: risk detection, risk assessment, risk minimisation and risk communication[9] A product is considered to be “safe” if it has an appropriate benefit-risk balance for the intended population and use i.e. if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects[10]

The goal of therapeutic risk management is to optimize the benefit-risk balance of a drug immediately after product launch. To be more specific, it can be elaborated as an interactive process of (1) assessing a product’s benefit-risk balance, (2) developing and implementing tools to minimise its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimisation tools to further improve the benefit-risk balance[10]. Such "adjustments" are often incorporated into communication plans. Risk minimisation consists of interventions

beyond labelling that aim at optimizing the benefit-risk profile of drugs. Examples of RMI are communication materials and restricted distribution programs (also referred to as Risk Evaluation and Mitigation Strategies, REMS, in the US) [10].

1.3 Current challenges in risk detection and risk minimisation processes

1.3.1 Risk detection challenges

The limitations of pre-approval clinical trials at identifying AEs are well-known, mainly due to the restrictive inclusion/ exclusion criteria of trials which generally exclude individuals with certain co-morbidities and concomitant medications, as well as special populations such as children, pregnant women, and elderly patients [11]. Clinical trials also tend to enrol limited numbers of subjects, usually a maximum of a few thousands, which are inadequate to identify rare AEs or those with long delays of onset [12]. Furthermore, trial populations include patients with a pre-specified indication, which does not permit the study of off-label use, an important component of drug safety surveillance [11]. As a result, identification of many safety risks has historically occurred in the post-marketing setting through pharmacovigilance activities[13]..

Pharmacovigilance is generally based on spontaneous reporting data: AEs are reported to pharmaceutical companies or regulatory organisations, by health care professionals (HCPs) or consumers who suspect that they may be experiencing a treatment-related medical event. As beneficial as these spontaneous reporting systems have been at identifying risks, they also have well-known limitations; the primary one being “underreporting” as in many instances HCPs or patients do not report these “side effects” as they do not “suspect” that they could in fact be due to the medications [14]. Other deterrents to reporting include time to complete the reporting form and lack of knowledge of surveillance systems [15]. Furthermore, in Canada and

most parts of the world, this process is voluntary, meaning that in many immeasurable cases even suspected[15] AEs may not be reported. Reporting is also influenced by factors such as previous knowledge about a risk (i.e. "listed" effects), severity of the drug, and time since marketing.

Central to signal detection through spontaneous reporting is the causality assessment: the evaluation of the likelihood that a particular treatment is the cause of an observed AE [16,17]... With the presence of a positive causality assessment, the evidence of association between AE and event is high, and the identification of a new risk by spontaneous reporting implies a strong association between the drug treatment and the occurrence of the event[18] Thus, even a few well-documented cases can lead to generation of a signal, despite the under-reporting limitation of SRS [19]. In fact, the withdrawal from the market of many drugs has been due to reports of safety risks identified through SRS [20,21]. Examples of such drug-AE pairs include: fenfluramine for cardiac valvulopathy, terfenadine for drug interactions/ventricular arrhythmias, troglitazone for hepatotoxicity, cisapride for drug interactions/ventricular arrhythmias, astemizole for drug interactions/ventricular arrhythmias, cerivastatin sodium for rhabdomyolysis, and efalizumab for progressive multifocal leukoencephalopathy[22,23,24,25].

Other methods of safety surveillance include meta-analyses of randomized clinical trials. Some of these clinical trials may be post-marketing clinical trials that are organised to study the long-term safety of a medication, a new indication of the drug, or to provide additional supporting data of safety risks identified from SRS [21]. Some regulatory withdrawals that were based on results of randomized clinical trials include: alosetron hydrochloride for ischemic colitis and complications of constipation, encainide due to excess mortality,

aprotinin due to increased mortality risk, and rofecoxib due to myocardial infarct and stroke[22,23,24,25].

In addition to clinical trials and the spontaneous reporting process, pharmacoepidemiologic studies, (i.e. observational studies of the use and effects of drugs in large populations [26]) have been used as risk assessment/ evaluation tools in order to further characterize risks initially identified by safety surveillance systems [27]. Hence, traditionally, these studies have been conducted in a "reactive" mode, i.e. after a signal has been detected in the real-world. This was rather inefficient since it involved lengthy processes to gather adequate data for accurate and reliable results. Consequently, before risk management, the timeline for risk detection, characterisation, and evaluation processes, was long.

The act of looking for and /or identifying new adverse events (AEs) or signals is known as signal detection (SD) [5]. As an attempt to improve the efficiency and the timeliness of the systems in place, data mining was introduced. Data mining is a process that supports SD by using computerised algorithms to discover hidden patterns of potential signals in large databases[28]. Most data mining algorithms have been implemented in national spontaneous reporting databases or databases of pharmaceutical companies. However the national spontaneous database in Canada is too small to perform quantitative data-mining, as it contains only about 225,000 suspected adverse reaction reports that occurred in Canada during the 46 years between 1965 and 2011, and data mining is currently not conducted in Canada [29]. Recently, attempts have also been made world-wide to use administrative claims database to conduct data mining[30,31,32]. Provincial claims databases are widely available in Canada (e.g. the Ontario Health Insurance Plan (OHIP) database, the Régie de l'assurance maladie Québec (RAMQ) database of Quebec, the Saskatchewan Drug Plan and Extended Benefits database amongst the most well-known) and have been extensively used for

pharmacoepidemiologic studies [33]. These databases include information on all prescribed medications dispensed to the members of the public drug program as well as all physician-patient encounters that are billed on a fee for service [34]. This results in an accumulation of longitudinal data on drug exposures and AEs on very large segments of the population[35]. Consequently, they may be a useful tool for signal detection in pharmacovigilance. Data mining using administrative claims databases has been conducted in large US databases but, to our knowledge, not in Canadian databases.

1.3.2 Risk minimisation challenges

Following risk detection and risk evaluation activities, strategies to minimise the identified risk(s) may be enacted if deemed necessary. These would normally be in the form of risk minimisation interventions (RMIs), which are beyond product labelling[35]. RMIs are tools which aim at reducing the risk of AEs among patients using medications, while preserving their benefits throughout the drug's life cycle[10]. Their main functions are to:
i) Communicate particular information regarding optimal product use ii) Provide guidance on prescribing, dispensing, and/or using a product in the most appropriate situations or patient populations. Examples of RMIs include Dear Health Care Professional letters, safety warnings, education programs, and restricted distribution, to name a few[10].

Although regulatory authorities have long ago issued guidance documents concerning pharmacovigilance (1991 in Canada), guidelines concerning therapeutic risk management have only been recently integrated into the regulatory process of the USA (2005), and Europe (2006) [10,9]. Although Canada has not yet integrated risk management into its drug regulation or legislation, it is reviewing risk management plans submitted by pharmaceutical companies.

Consequently, little is known about appropriate considerations in the establishment of RMIs. Due to the novelty of risk management, many drug manufacturers, as well as regulators, are still uncertain of what RMIs are available for use; which are appropriate for the various products; and what interventions should be incorporated in a particular product's risk management plan.

Chapter 2. Objectives and outline of thesis

This thesis addresses methodological gaps that currently exist in the published literature on therapeutic risk management, namely with respect to risk detection (identification), through a data mining study in a health claims database, and risk minimisation, through a systematic review of risk minimisation interventions.

Study I: Application of a Data Mining Algorithm to a Canadian Claims Database:

A data mining study was performed using the Quebec administrative claims databases (RAMQ) with the following objectives: i) To apply a data mining algorithm to support signal detection within the Quebec claims database; ii)To assess its performance through measures of sensitivity (detection of risk, and timeliness) and specificity; iii) To test the robustness of the tool in relation to different methodological considerations, namely with respect to the depletion of susceptibles effect and control for prescription channelling.

A retrospective cohort study was conducted in which a data mining algorithm was applied to a random sample of 87,389 elderly community-dwelling members of the Quebec public drug program (data from 1st January 2000 to 31st December 2009). Four known drug-AE pairs were analysed using the Maximised Sequential Probability Ratio Test (MaxSPRT), which compared monthly expected counts of AEs to observed counts of AEs. The time to detection of the potential signal using this method was compared to the actual historical date of the safety warning's posting by Health Canada. To determine the specificity of the method, two drug-event associations that were not considered to be a safety issues, were used as negative controls.

Study II: Review of Risk Minimisation Interventions in Drug Safety

Manuscript entitled: Impact of regulatory guidances and drug regulation on risk minimisation interventions in drug safety: a systematic review (accepted for publication in Drug Safety on December 28, 2011)

A systematic review (literature search and website search) of RMIs implemented between 1st January 2000 and 31st December 2009 was performed with the following objectives: i) To describe RMI type; year of RMI implementation; jurisdiction; and specificity of target population, target AE, and drug class; ii) Determine whether the introduction of guidances on therapeutic risk management had an effect on the characteristics of RMIs published in the literature or on regulatory agencies websites.

Together these studies and resulting publications are expected to serve as resources to identify methodological gaps of current RMIs, support signal detection, and provide new knowledge on data mining for the advance of drug safety surveillance within the Canadian population

Chapter 3. Signal detection in drug safety surveillance

3.1. Principles of signal detection

A key component of, and main reason for, pharmacovigilance is the act of looking for and /or identifying new adverse events (AEs) or signals[5] i.e. Signal detection .

The CIOMS VIII defines a signal as "Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action." [36].

The process of signal detection ideally begins at the product's introduction to the market. Nevertheless, in practice, it is carried out at various stages of a product's life cycle, such as when a safety concern is already suspected, or when monitoring for very serious safety risks of special interest[28].

This chapter provides a description of some components of signal detection: methods, data sources and finally a summary of some published studies that have been performed in the past.

There are two main methods for identifying safety issues: Qualitative Methods whereby experts manually review individual case reports, and Quantitative Methods or data mining involving the use of computerised algorithms to discover hidden patterns of associations or unexpected occurrences (i.e. 'signals') in large databases[28].

3.1.1 Qualitative methods of signal detection

Qualitative Signal Detection is the original form of signal detection in which experts manually review individual case reports to identify unanticipated effects [37]. In the past, this has been done using analyses and sometimes meta-analyses of case reports of randomized clinical trials, as well as the spontaneously reported AE case reports. Assessing the unexpectedness and causality of these events is a complex task, performed through a combination of activities including examining and comparing: patient characteristics, the underlying disease, as well as background rates of the event in the patient population [38]. For this reason collecting well-documented reports is extremely important with qualitative signal detection, and even just a few well-documented cases can lead to generation of a signal [14]. The causality (imputability) assessment: the evaluation of the likelihood that a particular treatment is the cause of an observed AE [16,17], is very important to the process of identifying signals qualitatively. Several methods have been developed to determine causality such as: the World Health Organisation (WHO) and Uppsala Monitoring Centre (UMC) tool for case causality assessment[16], which is used by many countries world-wide including Health Canada; the algorithm used by the AFSSApS (Agence française de sécurité sanitaire des produits de santé), commonly referred to as the "French causality assessment algorithm[39]"; and the algorithm used by the US Food and Drug Administration (FDA[40]). Common elements present within most causality assessment methods, that would allow for a compelling imputability analysis, are generally temporal sequence to onset of AE; previous drug-AE history; dechallenge/rechallenge information; and exclusion of alternative known causes e.g. concomitant medications [17], along with some additional criteria depending on the method. In general the causality assessment methods are very efficient except when used for

assessing AEs that have long delays of onset (e.g. cancer) or in populations where the AE is frequent. In these circumstances causality is difficult to establish.

Qualitative signal detection using few high-quality AE reports are not uncommon. In fact the temporary voluntary suspension of the drug natalizumab was performed after just two clinical trial reports of progressive multifocal leukoencephalopathy. The product was later reintroduced to the market with a strict risk management plan in place [41].

This traditional case-by-case qualitative assessment of reports continues to be, used effectively specifically in situations of low background rates of adverse event (AE) occurrence. However it poses a problem in instances where there is a very high amount of data, where the background rate of the AE in the population is high (i.e. too much background noise to be able to detect a signal), or there are complex associations such as drug-drug interactions. As technology progressed over time, computerised processes to support these tasks have developed, and quantitative methods for identifying safety findings, such as data mining, have become more common [42,43].

3.1.2 Quantitative methods of signal detection

Quantitative methods have become useful in instances of very high amounts of data, complex associations such as drug-drug interactions, or within populations where the background rates of AEs are high [28,42,44] . Consequently, data mining algorithms for signal detection have evolved as an integral component of the pharmacovigilance process in order to identify previously unknown adverse events (AEs) of a drug (i.e. Drug-event pairs or drug-AE pairs).

Quantitative methods can be divided into: i) Denominator-independent methods and, ii) Denominator-based methods. Both are based on disproportionality analyses (DPA) which examine the relative occurrence of observed drug-event pairs compared to an expected value based on overall reporting patterns [28,37,44].

3.1.2.1 Denominator-independent methods

With denominator-independent methods, rates of exposure to the drug of interest in the population are not required. These methods are very commonly used in national or company-sponsored spontaneous reporting (SR) databases which only possess reports of AEs. Consequently the exposure rates within the database are not an accurate reflection of the population's true exposure to the medication of interest (denominator[44]). Below is a description of the various denominator-independent methods found in the literature.

Frequentist (non-Bayesian) methods: These are the simplest approach to quantitative signal detection using disproportionality analysis. For each combination of drug-AE in a spontaneous reporting database, a two-by-two table of counts is obtained based on the number of reports involving the drug of interest (referred to as i) and the number of reports involving a specific AE (referred to as j), [45,46] . This is portrayed in Table I below.

Table I. Two-by-two table for frequentist methods in disproportionality analysis

Number of reports	**With drug i**	**Without drug i**	**Total**
With adverse event j	n_{ij}=a	b	a + b
Without adverse event j	c	d	c + d
Total	a + c	b +d	a + b + c + d

Many different forms of reporting ratios can be calculated and used to determine existence of a pair's disproportionality:

Relative Reporting Ratio (RRR) = [a/(a + b)] / [a/(a + c) / (a + b + c + d)]

Proportional Reporting Ratio (PRR) = [a/(a + c)] / [b/(b + d)]

Reporting Odds Ratio (ROR) = ad / bc

The PRR is analogous to a relative risk (RR) in a pharmacoepidemiologic cohort study, while the ROR is analogous to the Odds Ratio (OR) in a case-control study. Table II details advantages and disadvantages of quantitative methods described in this section[28].

Bayesian Methods: These compensate for areas where frequentist methods, described above, are lacking, i.e. by accounting for statistical uncertainty due to small counts[28]. Small counts are usually the case in a post-approval setting where AEs are rare. There are two main Bayesian methods. The first, used by the FDA and developed by DuMouchel, involves the technique of empirical Bayes screening (EBS) **[47, 48].** Mathematically it is based on a two gamma mixture distribution, and ranks drug-event combinations by degree of "interest" in terms of the number of reports of that particular drug-event pair, vs. what would be expected if the drug and event were statistically independent[44]

The two main formats of this method are the Gamma Poisson Shrinker (GPS) method, used when dealing with pair-wise associations of drug and AE (i.e. one drug, one AE) and the Multi-item GPS (MGPS)[49] method used when dealing with multi-item associations (e.g. Where two drugs in combination may be causing the AE) [50].

The second Bayesian method, used by WHO, is referred to as the Bayesian Confidence Propagation Neural Network (BCPNN) and involves calculation of an "information component" (IC) for each drug-event pair The formula of the IC comprises: i) the number of

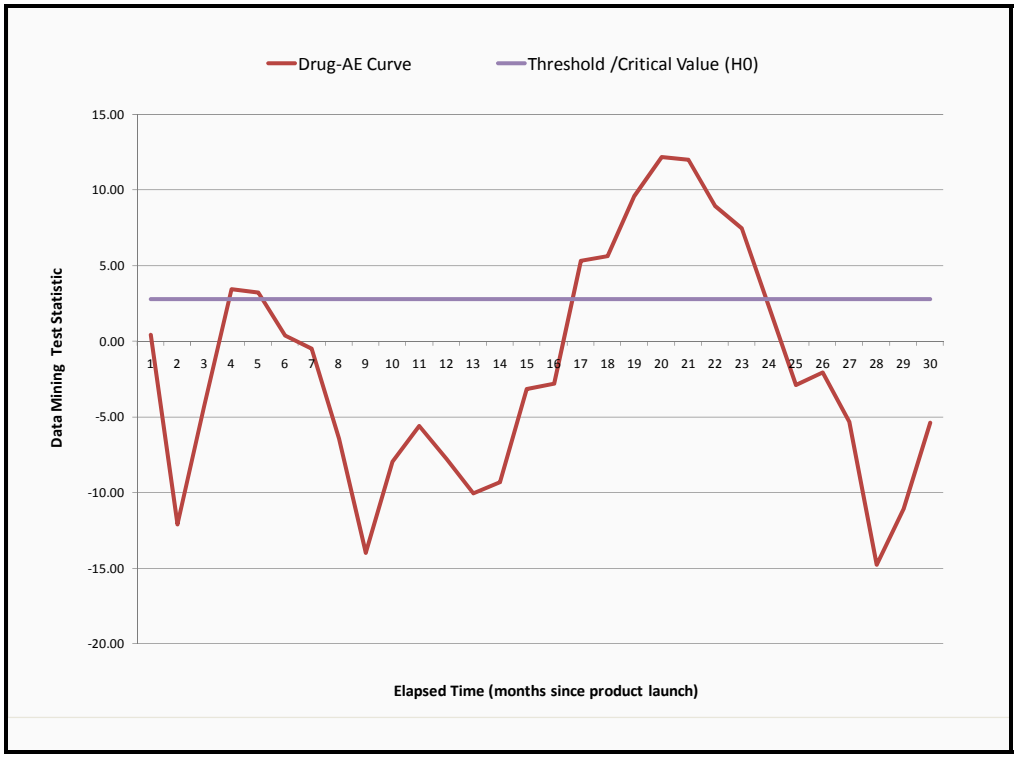
case reports with a specific drug, ii) the number of case reports with a specific AE, iii) the number of reports with the specific drug-AE combination, and iv) the total number of drug – AE reports in the database. In this way. the IC is a reflection of the value, precision and time trend of the information within the database. A positive IC value indicates that the particular combination of drug and AE is reported to the database more often than statistically expected, as compared to reports already present within the database[51].

3.1.2.2 Denominator-based methods

These are methods used when drug exposure rates are available, which then provide a "denominator" for the identification of disproportionality in the occurrence of AEs within the exposed group as compared to the occurrence of AEs in a reference group. Most often they are used to identify temporal changes in reporting rates or frequencies by constructing a probability model and a corresponding test statistic in order to assess the probability that the observed temporal changes reflect random sampling variability[44] .

Figure I below displays an example of a theoretical quantitative signal detection method. The number of patients using the medication of interest and experiencing a particular AE is compared to the number of patients using a reference drug product who also experience this AE. The point at which the users of the medication of interest appear to be experiencing a higher number/proportion of AEs than expected, is where a potential signal is said to be identified.

Figure I. Quantitative signal detection simulation example - Denominator-based



The two main denominator-based methods used on drugs are i) the Poisson method, and ii) the Sequential Probability Ratio Tests (SPRTs).

In accordance with the assumptions of the Poisson distribution [52], the Poisson method is used when the number of AEs is rare and occurs in large exposed populations. It requires three items of information: (i) Number of AE reports (observed), (ii) Estimated background incidence of AEs (number of expected cases) and, (iii) Estimated number of patients treated with the drug (i.e. exposure). Rare drug-event occurrences are modeled using estimated background incidence of an adverse event (AE) and the number of patients treated. This is done using a Poisson distribution to obtain the probability of obtaining coincidental drug-AE

associations per time period. Under various hypotheses of under-reporting, the expected number of cases will be compared to the observed number of cases, during the particular time period being studied. If the observed number exceeds the critical value in the Poisson distribution, then a signal is generated [44, 53].

The Sequential Probability Ratio Test (SPRT) is a sequential sampling technique used extensively in analyses of randomized clinical trial data. Also known as the classical or Wald's SPRT, it compares observed counts to expected counts in order to determine if a disproportionate number of events has occurred in the study group as compared to a reference/ control group. It is useful for safety monitoring on a weekly or monthly basis permitting early AE detection[54,55,56]. An AE signal would be generated if the log likelihood ratio (LLR) exceeds a pre-determined value, calculated based on a single alternative RR such as RR=2 (See example in Figure I). The key in this method is the fact that the p-values are adjusted for the multiple testing[57,58].

The Maximised SPRT (MaxSPRT) is a Poisson-based methodology that is an altered method of Wald's SPRT. Kulldorff[57] et al modified the test such that it does not require a specific "a priori" specification of a single level of increased risk that would define a signal (as with the classical SPRT). It instead uses a composite alternate hypothesis, H_A of Relative Risk (RR) >1[31]. In this way, it works well across the various ranges of RRs, and the test statistic, i.e. the log likelihood ratio (LLR) becomes a maximum likelihood under the composite alternative hypothesis divided by the likelihood under the null hypothesis H_0. (RR=1)[57]. Where:

$$LLR_t = ln(LR_t) = \max_{RR>1}((1-RR)\mu_t + c_t ln(RR)) = (\mu_t - c_t) + c_t ln(c_t/\mu_t)$$

It is useful for monitoring data of potential safety findings, on a weekly or monthly basis permitting early AE detection[54,55,56] and is broadly used in vaccine safety surveillance. The key being that the p-values of the continual/sequential analyses, are adjusted for the multiple testing[57,58].

Table II details the advantages and disadvantages of the various types of quantitative signal detection methods described in the previous section.

Table II. Summary of advantages and disadvantages of the various quantitative signal detection methods

Denominator-independent Methods		
Measure of association / Method	**Advantages**	**Disadvantages**
ROR [60,61]	*Covariable adjustments possible through logistic regression analysis *In logistic regression analysis, interaction terms can be used for the analysis of drug-drug and drug-disease interactions *Calculation and interpretation are straightforward (value>1 implies increased risk)	*Odds ratio cannot be calculated if the denominator is zero (i.e. either b or c = 0 in the two-by-two table) *Results not always reliable with small numbers in two-by-two table (see Table I)
PRR [61,62]	*Can still be calculated when c of the two-by-two table (see Table I) is zero *Represents a direct measure of the strength of the signal *Use of proportionate approach avoids potential biases related to underreporting if the overall level of reporting is high for a new drug *Can handle concomitant medication use by conducting subgroup analysis *Calculation and interpretation is straightforward (value>1 implies increased risk) *Easily implemented in standard software packages * Can handle covariate adjustment through stratification.	*Standard error cannot always be calculated *Cannot be calculated when a=0 in the two-by-two table (see Table I) *Statistical properties (e.g. sensitivity, specificity) of the standard signalling thresholds may vary when the methods are applied to different datasets. *A large association between an AE and a drug that is *not* of specific interest can reduce the likelihood of detecting a true signal * Cannot be calculated if there are no AEs of interest reported for the comparison drug(s) (i.e., if b=0 in two-by-two table (see Table I)). *Because it is a ratio of two proportions, its value is unstable with small sample sizes. E.g. when the AE of interest is rare, the PRR can easily miss detecting a signal when there is only one AE following the drug of interest
IC [61,62]	*Widely applicable to all data types (i.e. frequent or rare AEs)	*Difficult interpretation for those who are not familiar with Bayesian statistics

	*Large and complex numbers of calculations can be made efficiently *Can be used for pattern recognition in higher dimensions by arranging various drug–AE combinations in a single dimension for comparison) * Shown to be robust in handling incomplete data such as missing treatment indication, medical history and concomitant medications	
BCPNN [44,51,62,]	*Use of proportionate approach avoids potential biases related to variable underreporting. *Can handle concomitant medication use by conducting subgroup analysis *Use of the Bayesian framework provides for "estimate shrinkage" when the number of drug-AE reports is small, which can reduce the occurrence of false positive associations based on small sample variability. *Allows for the efficient application of large numbers of calculations as well as the application of logistic regression analysis to adjust for confounding and interaction factors	* Statistical properties (e. g. sensitivity, specificity) of the standard signalling thresholds may vary when the methods are applied to different datasets. * A large association between an AE and a drug that is *not* of specific interest (i.e. for large values of 'b' in the two-by-two table (see Table I)) can reduce the likelihood of detecting a true signal between that AE and the drug of interest.
MGPS [50,61,62]	*Use of proportionate approach avoids potential biases related to variable reporting) and underreporting. *Can easily handle concomitant medication use by conducting subgroup analysis *Use of the Bayesian framework provides for estimate 'shrinkage' when the number of drug-AE reports is small, which can reduce the occurrence of false positive associations based on small sample variability. * Uses Empirical Bayes methodology that is good at	*Statistical properties (e.g. sensitivity, specificity) of the standard signalling thresholds may vary when the methods are applied to different datasets. *A large association between an AE and a drug that is not of specific interest (i.e. for large values of 'b' in the two-by-two table (see Table I)) can reduce the likelihood of detecting a true signal between that AE and the drug of interest. *Elimination of confounders and limitations cannot be undertaken by any mathematical model

	minimizing the effect of sampling variance on the interpretation of the relative reporting rate. * Can handle covariate adjustment through stratification.	
Denominator-based methods		
Poisson method [44,61]	*Correction for different covariates can be easily established using poisson regression	*No measure of association is provided; only p-value to assess disproportionality *Only useful when studying rare events (i.e. assumption of the Poisson distribution)
Classical SPRT[54,57]	*Test statistic p-values are adjusted for the continual analyses of the data (i.e. multiple testing). *Allows for earliest possible analysis of AE signals.	*Requires a specific "a priori" specification of the level or magnitude of the increased risk *Test statistic can be difficult to interpret *Confounder adjustment in the literature is limited to method of stratification
MaxSPRT [57,63]	*Works well across various RR ranges due to its use of a composite alternative hypothesis of relative risk (RR) >1 rather than a single alternative hypothesis.	* Sensitive to uncertainties in estimated expected number of events *Test statistic can be difficult to interpret * Confounder adjustment in the literature is limited to method of stratification

3.1.3 Data sources for quantitative signal detection

3.1.3.1 Pharmacovigilance databases:

Spontaneous reporting (SR) databases created by regulatory authorities contain AE reports submitted by: pharmaceutical companies; health care professionals; and consumers. The most common regulatory SR databases include the Adverse Event Reporting System (AERS) being used by the US FDA, the United Kingdom's Yellow Card Scheme of the MHRA(Medicines and Health Care products Regulatory Agency), and the French national database of AFSSApS. In Canada, Health Canada maintains the Canada Vigilance database which is reviewed manually by clinical experts. In addition, in the EU (European Union), there is an ongoing initiative to create a central database for all member states, i.e. EudraVigilance [64] Although beneficial, these databases also have some disadvantages: i) since they include mainly spontaneous reports, they are subject to under-reporting, even in countries such as France with mandatory AE reporting. Under-reporting rates can vary between 36% and 99% [65,66]; ii) The quality, completeness and accuracy of reports can vary considerably; iii) There is difficulty in controlling for biases, such as indication or overall health status, to allow for adequate comparability of AEs across drugs[67]; and iv) They contain only ADRs creating a lack of accurate denominator (exposure) information and difficulty with the estimation of drug use. Furthermore, the coding of the ADRs may vary depending on the region of the database. Prior to 1997, the US FDA used the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART)[49]; while the majority of the rest of the world, including the national French database, previously used the World Health Organization's Adverse Reaction Terminology (WHO-ART) [68,69]. .

The majority of databases now use the international coding system initiative of the International Conference on Harmonization (ICH): the Medical Dictionary for Regulatory

Activities (MedDRA) the first version of which was released in 1995, and is currently at version level 14.1. However many databases possess coding from previous dictionaries for older reports (as with FDA AERS pre-1997 events), and yet other databases may be delayed in updating their coding dictionary to MedDRA [69,70]. The WHO adverse reaction database known as Vigibase continues to use the WHO-ART coding system [71].

Pharmaceutical companies also maintain safety databases. These are very similar to the regulatory databases except that they: (i) accumulate reports globally and (ii) are smaller and less diverse, as the reports are limited to company products. In some instances they may be too small, or the comprising products too heterogeneous, for meaningful analyses [28]. Table III details some SR databases and quantitative signal detection methods that have been applied to them.

Although it is mandated by Health Canada, most pharmaceutical companies input data in a company global database usually managed by the company head office (in either the United States or Europe), where data mining may be conducted. Health Canada does not conduct data mining directly in its Canada Vigilance database but rather incorporates Canadian cases in the global WHO adverse reaction database known as Vigibase. The WHO Vigibase is maintained by the Uppsala Monitoring Centre (UMC) in Sweden which, on a quarterly basis, applies a data mining method in order to identify potential safety signals [51]. There is only one record of a data mining study performed by Gavali et al[73] within the Health Canada database where although the signal detection test statistic values were high, a statistically significant signal was not obtained, possibly due to the small size of the database. The study authors recommended trying the signal detection processes again in larger databases[73].

Table III. Data mining studies using spontaneous reporting databases published in the literature

Authors	Year	Country	Database type	Database name	Method type	Method name
Bate et al. [74]	1998	Sweden / Global	Regulatory SR	WHO Vigibase	Denominator -independent	BCPNN
Lindquist et al. [51]	2000	Sweden / Global	Regulatory SR	WHO Vigibase	Denominator -independent	BCPNN
Evans et al. [75]	2001		Regulatory SR	UK Yellow Card System/ Adverse Drug Reactions Online Information Tracking (ADROIT)	Denominator -independent	PRR
Egberts et al [76].	2002	Netherlands	Regulatory SR	Netherlands Pharmacovigilance Foundation data base	Denominator -independent	ROR
Szarfman et al. [49]	2002	USA	Regulatory SR	FDA AERS	Denominator -independent	GPS & MGPS
van Puijenbroek [61]	2002	Netherlands	Regulatory SR	Netherlands PV Foundation Lareb	Denominator -independent	IC/ ROR / PRR Poisson/ Chi squared
van Puijenbroek [77].	2003	Netherlands	Regulatory SR	Netherlands PV Foundation Lareb	Denominator -independent	ROR
Hauben [78].	2004	USA	Regulatory SR	FDA AERS	Denominator -independent	MGPS

Authors	Year	Country	Database type	Database name	Method type	Method name
Hauben [79].	2004	USA	Regulatory SR	FDA AERS	Denominator-independent	
Schnell et al [80].	2005	USA	Regulatory SR	FDA AERS	Denominator-independent	PRR
Roux et al [81]	2005	France	Regulatory SR	AFSSAPS database	Denominator-independent	PRR
Thiessard et al [82].	2005	France	Regulatory SR	AFSSAPS database	Denominator-independent	PRR, ROR, SPRT, Yule's Q, Poisson method, IC, EBAM
Conforti et al [83].	2006	Italy	Regulatory SR	Italian Interregional Group of Pharmacovigilance (GIF) Database	Denominator-independent	PRR
Hochberg [84]	2007	USA	Regulatory SR	FDA AERS	Denominator-independent	A single data mining algorithm
Shalviri et al [85].	2007	Iran	Regulatory SR	Iranian Pharmaco-vigilance Database	Denominator-independent	ROR/ IC/ PRR
Lehman et al [42].	2007	USA	Company SR	Merck Post marketing safety database	Denominator-independent	Empirical Bayes method
Hammond et al [86]	2007	UK	Company SR	GSK Spontaneous reporting database	Denominator-independent	MGPS
Salvo et al [87]	2008	USA	Regulatory SR	FDA AERS	Denominator-independent	Case/ non-case (ROR)

Authors	Year	Country	Database type	Database name	Method type	Method name
Li et al [88]	2008	China	Regulatory SR	Guangdong ADR SRS	Denominator -independent	ROR / PRR/ IC
Chen et al [89]	2008	USA	Regulatory SR	FDA AERS	Denominator -independent	ROR / PRR/ IC/ GPS
Chen et al [90]	2008	USA	Regulatory SR	FDA AERS	Denominator -independent	ROR / PRR/ IC/ GPS
Li et al [91]	2009	China	Regulatory SR	Guangdong ADR SRS	Denominator -independent	IC
Poluzzi et al. [92]	2009	USA	Regulatory SR	FDA AERS	Denominator -independent	Case / non-case (ROR)
Ahmed et al [93]	2009	France	Regulatory SR	French PV DB	Denominator -independent	GPS / BCPNN
Gavali et al [73]	2009	Canada	Regulatory SR	Canadian Adverse Drug Reaction Monitoring Program DB	Denominator -independent	PRR
Hochberg et al [94]	2009	USA	Regulatory SR	FDA AERS	Denominator -independent	GPS / PRR
Alvarez et al [95]	2010	Europe	Regulatory SR	EudraVigilance	Denominator -independent	PRR
Chen et al [95]	2010	China	Regulatory SR	Jiangsu province SR DB	Denominator -independent	PRR / ROR / PNN

3.1.3.2 Prescription Event Monitoring (PEM)

PEM has been developed in the United Kingdom (UK) to monitor certain newly-marketed drugs and can be considered a hybrid of both spontaneous AE reporting; and administrative claims databases. It consists of a national observational cohort of first users of a drug immediately after its launch into real-world clinical setting, and a cohort of patients who receive a comparator drug[[97,98]. In the UK, health care is universal, with the majority of the population registered with a general practitioner (GP) who provides primary health care and writes prescriptions. The patient takes the prescription to a pharmacist who dispenses the medication and then sends a claim to a central Prescription Pricing Authority responsible for reimbursement of the pharmacist. The PEM system is handled by the Drug Safety Research Unit (DSRU) who is provided with electronic copies of all prescriptions issued throughout the UK for the drugs being monitored by PEM. After a period of three to 12 months (usually 6 months) from the first prescription for each patient, the DSRU sends a questionnaire to the prescribing physician requesting information on events which occurred since the drug was first prescribed, regardless of event causality. All data are computerised in the DSRU and important events are investigated by the DSRU personnel who, provided they have GP permission, possess the patient's life-time medical records, death certificate etc. For each of these patients the DSRU prepares a longitudinal record comprising all prescriptions for the monitored drug [98]. PEM has a numerator (the number of reports), a denominator (the person-time units of exposure), and a known time period (i.e. the difference between the start and stop dates of the drug for each patient)[98] .

The two quantitative methods that have been applied to PEM for signal generation are PRR and the incident rate ratio (IRR): a disproportionality measurement that compares the incident density of a particular event in a drug cohort with the incident density for that same event in a comparator group of other drug cohorts for which PEM studies have been conducted [99] .

With Incidence Density (ID) for a given time period, t for each event term in the DSRU dictionary, ID is calculated as follows:

ID_t = (Number of events during treatment period for t / Number of patient-months of treatment for period) X 1000 [98]

The limitations of PEM are that it relies on the voluntary participation of general practitioners (GPs), and cohorts are relatively small in size (usually about 10, 000 users of the drug of interest) (restricted ability to study rare AEs). As with most databases, there is no method of measuring compliance or the use of non-prescription medication [98,99] . Table IV below details some PEM studies.

Table IV - Quantitative signal detection studies performed through prescription-event monitoring found in the literature

Authors	Year	Country	Method Type	Method Name
Heeley et al [99]	2002	UK	Denominator-independent	PRR & IRR
Layton et al [100] .	2006	UK	N/A	IRR

3.1.3.3 Health claims databases

Administrative health claims databases have been created in the context of a drug and medical services reimbursement program. They include longitudinal medical records including information on: all prescribed medications dispensed to the members, and covered by the drug program; all physician-patient encounters and diagnoses; and in some instances, hospital admissions and laboratory results[33,34,38]. This results in an accumulation of longitudinal data on drug exposures and AEs on very large segments of the population.

Medical services database: In order to be reimbursed by the medical program, physicians submit reports on medical services provided (which may include, inpatient, outpatient, ambulatory, emergency and sometimes hospital services), as well as the diagnoses code, to the insurance provider for reimbursement. All services billed on a fee-for-services are recorded. Among the data elements included in this database are: the code of the diagnosis (most databases use the International Classification of Diseases (ICD) coding system versions 9 or 10), medical act rendered, the date, the location of the service, and, patient health insurance number [33,34].

Prescription database: Prescription drug databases record outpatient prescription drugs dispensed to the members of the health plan. The information recorded consists of: the generic name of drug, national drug code for dispensing, dispensing date, dosage, days supplied, route of administration and patient health insurance number [33,34,102].

Beneficiary database: This database contains information concerning demographic characteristics of the patient such as age/ date of birth, gender, region of residence (metropolitan, urban, rural), date range of membership in the insurance program, and patient health insurance number [33] .

Usually the medical services and prescription drug databases may be linked through a unique patient identifier/ patient health insurance number that remains unchanged over time and is scrambled by the insurance provider Linkage provides an accumulation of health care data on entire populations on a long term [34] .

Administrative health claims databases are available in Canada and have been used mainly for pharmacoepidemiologic studies [33] . Examples of these databases are those based on the universal healthcare established per province such as the Ontario Drug Benefits database, the Saskatchewan Health Services Databases, and the Régie de l'assurance maladie Québec" (RAMQ) database. In the US, there are Health Maintenance Organization (HMO) databases such as the private insurance companies of Kaiser Permanente, or the Medicaid program databases from the public health program (Medicare) consisting mostly of the elderly, or individuals on social assistance [103]. While observational studies are hypothesis-driven, signal detection is hypothesis-generating. The HMO databases have been used for quantitative signal detection but so far, no attempt has been made in Canadian databases[31,63]. Table V below also details some administrative claims databases that have been used in published quantitative signal detection studies. Advantages of claims databases, as a data source to conduct safety surveillance are the following: i) Potential to perform active or passive, and real-time surveillance; ii) Allowance for longitudinal

monitoring of large patient cohorts; iii) Potential to identify AEs with long latency; iv) Provision of both numerator and denominator information on the populations allowing for the estimation of drug use and disease incidence, as well as the evaluation of temporal relationships between the drug and AE[28].; v) Existence of a variety of patient-level information on covariables, allowing for the potential verification of signals through executing pharmacoepidemiologic studies.

With these databases, duplicate records can be easily identified and excluded by examining person or type-specific AE information, eliminating follow-up diagnoses codes, or accepting only the initial event diagnosis per patient identifier. Because the databases do not rely only on the reporting of AEs, they could provide information on real-world AE experiences, and have the potential to detect unrecognized or underappreciated AE signals as compared to SR databases [38,104,105] .

The limitations of using health claims databases include the potential for restricted generalisability as the population may be limited depending on the members of the insurance plan. E.g. private health insurance plans may exclude individuals of low socio-economic status. The RAMQ prescription plan covers primarily the elderly population. Furthermore, the follow-up of patients may be restricted as some patients may switch insurers every few years [103] .

The reliability of the ICD-9 or ICD-10 diagnostic codes reported by the HCPs may be problematic since validation is not required for reimbursement. However, the reliability may be improved using other data elements such as medical procedure or drug prescription as proxy for the presence of a disease.

Only those medications that are reimbursable by the particular health insurance plan would be available in the database for analysis. This would generally exclude over-the-counter medications, as well as some very new drugs that have not yet been reviewed and approved by the insurers.

Table V – Quantitative signal detection studies performed in administrative claims databases found in the literature

Authors	Year	Country	Database used	Method type	Method name
Brown et al [63]	2007	USA	9 different HMOs	Denominator-based	MaxSPRT
Choi et al [30].	2010	Korea	National Health Insurance Claims	Denominator-based	RR
Trifiro et al [32].	2011	Denmark, Italy, Netherlands, and United Kingdom	EU-ADR database (8 databases from Denmark, Italy, Netherlands, and United Kingdom		Various. GPS and others

3.1.4 Data elements required for quantitative signal detection using administrative claims databases

The data elements found in administrative claims databases that are needed to conduct quantitative signal detection are the following: i) a suspected drug (medication dispensed); ii) a suspected AE (using the diagnostic code in medical billings or in hospitalization databases) and; iii) an identifiable patient (scrambled identifier). Dispensing date and date of AE occurrence confirm that the exposure precedes an event. As shown in Table IV,

most of the studies published in the literature used diagnoses on medical claims, and not hospitalization, as the data source for AEs. For some AEs, especially those that are chronic, this timeline may be subject to errors given that there may be a delay between the date of onset of symptoms of the AE and the date of diagnosis.

3.1.5 Performance of data mining algorithms for drug safety signal detection

Prior studies published in the literature indicate that the main means of assessing performance of data mining algorithms are through: i) Ability to generate a signal in cases of a known drug-AE pair (true-positive; sensitivity), ii) Comparing the time to detection of the potential signal between traditional signal detection and quantitative signal detection method [49,74,75]; iii) Statistically significant measures of association in the absence of a true signal (false-positive; specificity).

Results of studies published in the literature on the performance of data mining algorithms are described below.

A study by Szarfman et al [49] was conducted using the FDA's safety database, AERS. The GPS method was used to examine differences in year of detection of 30 known drug-AE signals. Data mining identified 30 signals as positive, 20 signals were identified using the data collected 1 to 5 years before the signals had been detected by standard methods, nine the same year and one signal 1-year after. GPS was also used to explore the differences in

time of detection of 160 drug-AE signals between 1985 and 1996 that had previously been identified in the Center for Drug Evaluation and Research CDER Monitoring Adverse Reports Tracking System. , Using the method and the data collected, 97 positive data mining signals were detected, 1 to 4 years before they were historically identified as signals. 36 the same year, and 27 of them 1 to 3 years later. This study demonstrated that a retrospective data mining of this database using the GPS and MGPS (GPS results compared to previous MGPS study) methodologies identified AEs many years earlier than qualitative signal detection through case reports alone[49].

Through the PRR methodology, the UK Yellow Card Database as a data source for signal detection was shown to be a valuable aid to signal generation. In Evans et al [75] , 15 newly marketed drugs were analysed. They first examined whether the method would identify known hazards, before looking at possible AEs which had not yet been recognized. Using this methodology, 481 signals were observed that met inclusion criteria (i.e. a PRR >=2, a chi^2 value >=4, and the existence of three or more cases of the drug-AE pair being studied), 70% of these were found to be AEs already identified, 13% were believed to be related to the underlying disease, and 17% required further investigation. Approximately five unrecognized signals per drug were identified using the method [75].

The Netherlands Pharmacovigilance Foundation has used the data mining methodology of ROR to identify three drug-AE pairs i) antidepressant drugs and non-puerpural lactation; ii) non-steroidal anti-inflammatory drugs with diuretics, and onset or worsening of congestive heart failure; and iii) terbinafine- with occurrence of arthralgia, fever and urticaria [76].

The analysis of association between antidepressant drugs and the occurrence of non-puerpural lactation. demonstrated that 38 cases of non-puerperal lactation were reported, of which 15 were associated with the use of antidepressant drugs. Antidepressants overall were associated with a higher risk of non-puerperal lactation as compared to other drugs (ROR 8.3; 95% CI 4.3 to 16.1). Serotonergic antidepressants were associated with a higher risk (ROR 12.7; 95% CI 6.4 to 25.4), while other antidepressants were not (ROR 1.6; 95% CI: 0.2 to 11.6) compared with the group of all other drugs.

The onset or worsening of congestive heart failure (CHF) associated with the combined use of non-steroidal anti-inflammatory drugs (NSAIDS) and diuretics was also tested as an example of a drug-drug interaction. The analysis showed that the use of diuretics or NSAIDs itself was not statistically significantly associated with an increased risk for onset or worsening of symptoms of CHF. However, the odds ratio of the statistical interaction term NSAIDs-diuretics, was statistically significantly elevated (adjusted ROR 2.0; 95% CI 1.1 to 3.7)

To study a possible relationship between fever, urticaria and arthralgia, ROR were calculated, which were adjusted for age and gender of the patients, source of the reports and year of reporting. Both urticaria (adjusted ROR 1.72; 95% CI 1.35 to 2.18) and arthralgia (adjusted ROR 3.14; 95% CI 1.52 to 6.47) were significantly associated with reports on terbinafine. The strongest predictor covariates of the dependent variable were urticaria (adjusted ROR 1.66; 95% CI 1.29 to 2.14) along with the interaction terms arthralgia and fever (adjusted ROR 2.35; 95% CI 1.32 to 4.17) and arthralgia-urticaria (adjusted ROR 3.33; 95% CI 1.03 to 10.73). These results imply an association between the use of the antifungal agent terbinafine and the co-occurrence of arthralgia, fever and urticaria [76].

Bate et al. used the WHO UMC database and the BCPNN methodology to create signal detection method to provide initial assessment, selection, and act as a quantitative aid to signal detection of drug-AE combinations, consequently allowing for the consistent detection of new AEs [47,51]. In this study they conducted initial testing of the data mining approach examining whether the test statistics were positive for drug-ADR combinations already known to exist and that it was non-significant for drug-ADR combinations known not to exist [74]. Tests to determine whether earlier signals would have been found with the new method were then conducted both against general reference sources (Physicians' Desk Reference and Martindale) and existing literature reports in another sensitive international signalling system database of the publication Reactions Weekly)[74]. The study displayed the power of the method at finding signals early (captopril-coughing) and to avoid false positives signals with the occurrence of common drugs and ADRs in the database (digoxin-acne; digoxin-rash). An application of the BCPNN on quarterly data showed that out of 1,004 AEs identified, 12 were found to be new AEs not already recorded within regulatory documents [74]

Many studies have also been published with the French national database, mainly using the PRR method. Roux et al [81] applied the PRR to the French national pharmacovigilance database, AFSSAPS in order to statistically identify potential signals of previously unknown drug-AE associations, using criteria of a PRR >=2, a chi^2 value >=4, and the existence of three or more cases. Statistically significant drug-AE associations were verified against the Vidal (French drug reference) dictionary. Associations not previously listed in the dictionary were considered as potential signals. Application of the data mining

algorithm produced 523 drug-AE associations of which 107 were not listed within the Vidal dictionary, and considered potential signals. Most potential signals were false positives. The process helped focus case review on a very small subset (9.6%) of the dataset [81].

Thiessard et al [82] compared the methods of PRR, ROR, SPRT, Yule's Q, the Poisson method, IC, and EBAM (empirical bayes arithmetic mean) within the AFSSAPS database. The resulting number of signals generated varied with each of the methods used, however was high for each. Using SPRT, 6.3% of all drug-AE pairs in the database, were considered as signals 9.1% were considered signals with the EBAM method. The remaining methods generated signals for between 18.7% and 33.6% of drug-AE pairs within the database. A comparison of ranked percentiles showed quasi-equivalence between the methods of PRR, ROR and Yule's Q. The PRR was found to be more effective with small sample sizes as compared to the EBAM, the Poisson method and the SPRT : the PRR generated significant signals for pairs that were reported just once or twice within the database, which were not identified with the other methods. However, the IC, and Yule's Q were less sensitive to small numbers than the PRR[82].

Performance of quantitative signal detection methods was also assessed in administrative claims databases. In a study conducted by Brown et al[63]., nine different administrative databases of the HMO Research Network's Center for Education and Research on Therapeutics (CERT) and the MaxSPRT methodology were used. It was shown that four out of five of the known drug-AE pairs studied, did indeed produce a signal using the

methodology, which is indicative of a favourable sensitivity [63]. No signal of excess risk was identified for the two negative control pairs, implying that the specificity of the method was also adequate.

Choi et al[30] used a Korean national health insurance claims database and a RR-based methodology for signal detection of rosuvastatin AEs. Any serious adverse event (SAE) for which the lower limit of the RR's 95% confidence interval was greater than 1, was defined as a signal. All detected signals were reviewed to determine whether the signals corresponded with published AEs exclusive to rosuvastatin. Among 96 236 elderly outpatients who received rosuvastatin, or other statins, 376 different SAEs were observed, and 40 304 drug-SAE pairs were observed. Twenty-five (6.6%) drug-SAE pairs were detected as signals [30].

Sensitivity within the Szarfman et al[49] study, was estimated by counting current labelled events or current warnings and contraindications signalled by any mapped AE code: number of detected AEs/(number of detected AEs + number of undetected AEs).

Specificity was estimated by counting individual AE codes that did not map to a labelled event i.e. number of true negative/ (number of true negative + false positive). The study showed a high degree of specificity for all thresholds used since the first signals were detected by MGPS. The sensitivity for warnings and contraindications was higher than the one observed for the analysis across all labelled events. Lowering the thresholds for important event codes or detecting higher order synergic associations between drugs and multiple events increased sensitivity[49].

Hochberg et al[84] in a study comparing GPS, PRR, and a urn model, analysed sensitivity and specificity, by establishing and using rules for assigning each drug-AE combination to an approximate "level of evidence" to describe the strength of evidence for causality contained in the corresponding information source. The GPS method had the highest specificity in that it had the highest rate of matching against the reference event database for drug-event associations with at least minimal external supporting evidence. However, GPS also detected the smallest number of signals and did not uniquely highlight any unlabelled supported signals. The PRR method detected the highest number of unlabelled supported and unique unlabelled supported signals followed by the urn model[84].

Choi et al[30] calculated the PPV of their method by dividing the total number of the signals known to be published as AEs, by the total number of detected signals. Of 25 signals detected by the RR-based data-mining approach, eight corresponded with published rosuvastatin-specific AEs, with a PPV of 32%. When detected signals were compared to other statin-specific or shared list of AEs from the reference literature, 18 signals corresponded. The PPV was estimated to be 80%.

In the Brown et al study[63], sensitivity and specificity were relatively simple concepts in that detecting a signal where a known safety risk occurred (4 out of 5 cases) was deemed a "good sensitivity", and not detecting a signal in instances where a safety risk was known not to exist (2 out of 2 case studies), was implied to indicate a "good specificity".

Data mining and signal detection are hypothesis-generating activities in that any potential signal generated would need to be further analysed, investigated and verified in order to confirm that a signal does indeed exist. The main limitation of data mining is the generation of a large number of false-positive signals, each requiring further analyses. As such, many jurisdictions and companies do not invest the resources in conducting data mining, as investigating each signal could be quite inefficient [5].

In conclusion, this literature review shows us that qualitative signal detection through spontaneously reported case studies, and clinical trials, has become inadequate at identifying signals on its own. New methods to quickly identify safety risks are an important necessity in order to protect patients from unwanted AEs.

From Tables III and IV, and the study descriptions above, it is observed that most data mining studies have been conducted in SR databases, using denominator–independent methodology. Few studies have been applied to administrative claims databases using denominator-based methods, even fewer have attempted to apply a sequential monitoring approach to quickly identify safety risks after product launch, and none such studies have been conducted using a Canadian health care claims database. In addition, there are important gaps in the data mining and signal detection processes that should be addressed such as further exploring the potential of sequential monitoring / early signal detection, and investigating additional means to control for confounding.

Provincial health care claims databases are widely available in Canada and may be a useful tool for the application of denominator-based data mining algorithms to support signal detection in pharmacovigilance.

Chapter 4. Quantitative signal detection using the Quebec administrative health care claims databases

4.1 Rationale

Quantitative signal detection is currently not performed in the national spontaneous reporting database of Canada (Canada Vigilance) due in part, to small sample size and insufficient resources to substantiate all signals that are detected. Provincial health care claims databases are widely available in Canada. In Quebec, the claims databases include the prescription drug database as well as the medical services database, both being administered by the Régie de l'assurance maladie du Québec (RAMQ). The prescription drug database includes all prescribed medications that are covered by the public program and that are dispensed to drug plan members. The medical services database includes billings by physicians on a fee-for-service, whether the service is rendered in an outpatient, inpatient, or emergency room setting. Both databases are populated on a real-time basis, i.e. the information is entered and transmitted either at the time of the service (pharmacy dispensation) or soon after (physician billings). A hospitalization database, Med-Echo, is also available in Quebec which records information on hospital discharges from the great majority of hospitals. Although it provides accurate information on diagnoses, its usefulness for signal detection is questionable given that it is populated only once per year.

Data elements found in the prescription database and the medical services database provide information on drug exposure and occurrence of adverse events. Linkage between the two databases is conducted through the patient's health insurance number, which remains unchanged over time. Such linkage allows for the accumulation of longitudinal population data on drug exposure and occurrence of adverse events on a very long term.

Since the great majority of elderly residents of Quebec are covered by the public drug program, the resulting database is very comprehensive and provides optimum generalizability. In addition, from a therapeutic risk management perspective, the elderly population has been identified as a high-risk population by regulatory authorities, and as such, involve a dedicated section in risk management plans of drug products [10].Their increased susceptibility for medication-induced adverse events, morbidity, and mortality may be due to several factors such as metabolic changes, comorbidity, concomitant drug usage, and consequently an increased potential for drug-drug interactions[106]. Although the ICH specifies requirements for clinical trials in instances where a product is expected to be used by the elderly [107], there is still an important evidence gap at the time of product approval for drugs not intended for use in the elderly, and those that may be used off-label in this group, given that the elderly are rarely included in randomized controlled trials that are conducted prior to approval of such products. They are therefore considered, in many instances, as subjects of safety surveillance activities in the post-approval setting. The prospect of using a data source, such as the claims databases of the “Régie de l’assurance maladie Québec” (RAMQ), which contains approximately 97% of the province’s elderly population, is likely enviable of the fields of data mining, PMS, and pharmacovigilance

overall [108].A tool focusing on the geriatric patient population shall prove highly relevant to support the detection of safety signals in a real life setting.

Studies found in the literature have shown that claims databases may be a useful tool to support safety signal detection[30,63]. Analytical tools vary, however, with respect to their applicability. Some of the tools have been developed specifically for the surveillance of previously identified risks[63], i.e. in the setting of an active surveillance program, and as such require the exclusion of patients who have experienced the adverse event of interest in the recent past. Others[30,64] do not require such exclusions given that they have been developed for passive surveillance purposes, i.e. with the objective of uncovering previously unknown adverse effects. To our knowledge, the usefulness of claims database to support safety signal detection in the context of a passive or active surveillance program has never been compared.

Furthermore, published studies have used a limited number of covariates in their model, consisting mainly of age and sex. Conversely, in the field of pharmacoepidemiology, there has been a dramatic methodological development over the past decade, with advanced methods for summarizing and adjusting for confounders measured or unmeasured in claims databases. Applying any of these methods to control confounding in a signal detection study would represent significant progress in this area of research.

Over the past two decades, the Quebec administrative claims databases have been used extensively to conduct drug utilization and risk evaluation studies, i.e. hypothesis-testing studies. To our knowledge, they have not yet been used to support safety signal detection, i.e. hypothesis-generating studies.

4.2 Research hypothesis

Existing data mining algorithms would be applicable to the Quebec administrative claims databases and would be successful at detecting drug safety signals.

4.3 Study objectives

4.3.1 Main objective

To apply and validate a data mining algorithm for signal detection using the Quebec prescription and medical services databases.

4.3.2 Specific objectives

1) To apply the MaxSPRT data mining algorithm to support signal detection, within the Quebec claims database;

2) To assess the tool performance through measures of sensitivity and specificity;

3) To determine whether adjusting for patient overall health status improves the performance of the tool

4) To offer methodological improvements over existing data mining models that have been published in the literature

4.4 Methods

4.4.1 Study design

A retrospective cohort study was conducted in a random sample of 87,360 community-dwelling elderly members (age 66+) of the Quebec public drug program identified from 1st January 2000 to 31st December 2009. The Poisson-based Maximised Sequential Probability Ratio Test (MaxSPRT) was used as the data mining algorithm. Four known drug-AE pairs, for which there was a safety warning issued by Health Canada during the study period, and two drug-AE pairs not known to be associated ("negative controls") were used. Covariates included: age group (66-69; 70-74, 75-79, 80-84, 85+),gender (dichotomous), Chronic Disease Score (CDS) (grouped into: 0; > 0-<5; ≥5 - <10, ≥10). The analytical method is an adaptation of the method developed by Brown et al[63] with the following methodological improvements: i) the consideration of the depletion of susceptibles effect; ii) further adjustment for confounding by overall health status, through the von Korff Chronic Disease Score, based on prescription drug use. Furthermore, the applicability of the method for active or passive surveillance was determined, respectively, by excluding and including patients with a history of the adverse event. Each of these methodological aspects is described in greater details in the sections below.

4.4.2 Selection of drug-adverse event pairs

The following criteria were used to select four known drug-AE combinations:

i) Involve drugs used commonly in the elderly population

ii) Approved by Health Canada and included in the list of reimbursed medications of Quebec within the study period cohort (January 1, 2000 - December 31, 2009).

iii) Subject of Health Canada Warnings that were published during the study period

The criteria used to select a comparator drug for each study drug chosen was as follows:

i) Also approved by Health Canada and included in the list of reimbursed medications of Quebec within the study period cohort

ii) Also used commonly in the elderly population

iii) Used for the same indication as the study drug in order to control for indication bias

iv) AE of interest was not listed in the comparator drug's Product Monograph as a potential adverse reaction of the comparator drug

The criteria used to select the negative-control drug-AE combinations were as follows:

i) Also approved by Health Canada and included in the list of reimbursed medications of Quebec within the study period cohort

ii) Also used commonly in the elderly population

iii) AE of interest chosen was one that was a) relatively serious / medically significant, b) not listed on the product monograph of the study drug, c) Possessed relatively clear and concise ICD-9 codes and d)Occurred with relatively common frequency in non-users of the drug of interest (in order to optimize statistical power)

The criteria used to choose comparator drugs of the negative-control pairs were:

i) Involved drugs used commonly in the elderly population

ii) Approved by Health Canada and included in the list of reimbursed medications of Quebec within the study period cohort

iii) AE of interest was not listed on the product monograph of the comparator drug

Because no association was expected with these pairs, it was not necessary to choose a comparator drug used for the same indication as the study drug in the negative-control pairs.

Table VI – Drug-AE case studies used in data mining analysis

Drug-AE pair	**Comparator Drug**	**Date of Health Canada Warning (where applicable)**
1. rosuvastatin- rhabdomyolysis	Other statins: atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin	June 2004
2. rosiglitazone- Cardiac safety concerns	metformin	November 2007
3. rosiglitazone – Increased fractures in female patients	metformin	February 2007
4. pioglitazone-Increased fractures in female patients	metformin	April 2007
5. amitriptyline –increased fractures (negative-control)	metoprolol	N/A
6. alendronate – acute hepatitis (negative-control)	atenolol	N/A

4.4.3 Data sources

The following RAMQ databases were used to conduct the study: i) the prescription database; ii) the medical services database; iii) the beneficiary database.

Prescription database*:* In Quebec, the public drug programs includes approximately 97% (circa 800,000) of elderly residents, all welfare recipients, as well as all residents and their dependents who are not covered by a private drug insurance (approximately 30% of residents aged 18-64). The database records information on all outpatient prescriptions included in the formulary of reimbursed medications: Drug name, dispensing date, dosage, prescribed duration, number of units dispensed, route of administration, deductible and co-payment. Drug indication is not recorded. Drugs acquired in-hospital, over-the-counter, or out-of-pocket, are not covered by the public drug program and hence, are not included in the RAMQ prescription database.

Medical services database*:* Due to Canada's universal health care system, medical services, including consultations, examinations, procedures, among others, are provided free of charge at the point of service to all residents of the province, regardless of age and income. The resulting medical services database contains information that physicians submit to RAMQ for reimbursement of fee-for-service, whether rendered in an inpatient, outpatient, or emergency department setting. Exceptions are services rendered by a minority of physicians who are on a salary basis. Among the information included in the database are: date and location of the medical service, nature of services (coded according to the Federation of General Practitioners of Quebec (FMOQ), the Federation of Specialist Physicians of Quebec (FMSQ), the Canadian Classification of Surgical Acts etc.), and diagnosis (coded according to ICD-9). The latter, however, is not obligatory for reimbursement and when present, its reliability may be questionable [109].

Beneficiary database*:* For each resident of the province, the beneficiary database contains information concerning patient demographics: age (for confidentiality reasons, recorded in 5-year intervals), gender, residential region (recorded as CLSC (Centre local de services communautaire) region) and dates of membership in medical services and drug programs. Through the level of deductible and co-payment, one can derive gross measures income status.

The RAMQ databases may be linked through the patient health insurance number, which is unique for each patient and remains unchanged over time. The RAMQ databases are populated in near-real time, and hence theoretically would be available to conduct prospective drug safety surveillance.

4.4.4 Populations

4.4.4.1 Target population

The target population consists of community-dwelling elderly residents (age 66 +) of Quebec. A cut-off at age 66 was set since claims data are required for one year prior to their inclusion in the study, and the public drug program is comprehensive starting solely at age 65.

4.4.4.2 Source population

The source population consisted of a random sample of 87,389 elderly patients (age 66+) who were members of the RAMQ public drug plan between 1st January 2000 and 31st

December 2009. Since it was a random sample, no specific event led to entry in the cohort. The date of entry was randomly chosen, for each individual, during the study period and the period of membership in the drug program. For the investigation of signals related to alendronate, the study population was restricted to females only. All members of the cohort were followed until the first of the following events: i) death, ii) institutionalization, iii) end of coverage in drug program; iv) end of study period (31 December 2009).

4.4.4.3 Study population

Five sub-cohorts of incident users of the exposure drugs described in section 4.4.2 above were assembled (i.e. rosuvastatin, rosiglitazone, pioglitazone, amitriptyline, alendronate). For each cohort, incident use was defined as absence of dispensing of the drug during the year prior to current treatment. The use of incident exposure aims at controlling for potential depletion of susceptibles effect, whereby long-term users of a drug are at lower risk of the AE than new users [110].This is consistent with the new-user design [111]. Section 4.4.10 below "Control of biases" describes this phenomenon in further detail.

The index date for the exposed groups was the date of first dispensing of the drug of interest during the study period. Contrary to published studies (Brown et al [31,63]), for the main analyses, history of the AE of interest for a given drug-AE pair was not an exclusion criterion given that in a true passive safety surveillance setting, it is not known which event will occur. Exclusion of such patients will be addressed in a sensitivity analysis described below (section 4.4.11).

4.4.5 Follow-up

For the signal detection models, subjects were followed until the first of the following events: i) Three months after the date of treatment (sensitivity analyses of six months and 12 months) ii) Switching to the comparator drug; iii) Occurrence of the AE; iv) End of drug treatment (+14 days residual risk period); or v) Death, institutionalization, hospitalization (as drugs dispensed in-hospital are not recorded in the RAMQ prescription database), vi) End of coverage in public drug or medical services program, vii) 31st December 2009.

4.4.6 Study variables for each drug-adverse event pair

Appendix I summarizes the variables of this study, and codes used for their acquisition.

4.4.6.1 Rosuvastatin – rhabdomyolysis

Dependent variable

ICD-9 codes for rhabdomyolysis was 728.8 in the RAMQ medical services database.

Independent variable

The "code denomination commune" for the study drug of rosuvastatin (46860) and for the comparators of "other statins" (47232; 47609; 47083; 47604; 45500; 45570; 47595; 45564) from within the RAMQ prescription services database were used.

4.4.6.2- Rosiglitazone – acute myocardial infarction

Dependent variable

ICD-9 codes for the AE of acute myocardial infarction: 410, 410.0, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8 and 410.9 in the RAMQ medical services database. Codes related to follow-up were excluded,

Independent variable

The "code denomination commune" for the study drug of rosiglitazone (47371, 47652, 46642) and for the comparator of metformin (05824; 47208; 47807) from within the RAMQ prescription services database.

4.4.6.3 Rosiglitazone - increased fractures in female patients

Dependent variable

ICD-9 codes for the AE of fractures: 800 to 829 and 733.1, in the RAMQ medical services database.

Independent variable

The "code denomination commune" for the study drug of rosiglitazone (47371, 47652, 46642) and for the comparator of metformin (05824; 47208**;** 47807) from within the RAMQ prescription services database.

4.4.6..4- Pioglitazone-increased fractures in female patients

Dependent variable

ICD-9 codes for the AE of fractures: 800 to 829 and 733.1, in the RAMQ medical services database.

Independent variable

The "code denomination commune" for the study drug of pioglitazone (46678; 47392) and for the comparator of metformin (05824; 47208; 47807) from within the RAMQ prescription services database.

Negative-control drug-AE pairs

4.4.6.5- Amitriptyline – increased fractures in female patients

Dependent variable

ICD-9 codes for the AE of fractures: 800 to 829 and 733.1 in the RAMQ medical services database.

Independent variable

The "code denomination commune" for the study drug of amitrptyline (00429 ; 00442 ; 46011) and for the comparators of metoprolol (38275, 46763,46780) from within the RAMQ prescription services database.

4.4.6.6- Alendronate – acute hepatitis

Dependent variable

ICD-9 codes for the AE of acute hepatitis: Acute hepatitis 573.3 & 570.x in the RAMQ medical services database.

Independent variable

The “code denomination commune” for the study drug of alendronate (46295; 47165; 43670, 47662; 47747) and for the comparators of atenolol (46315; 46325) from within the RAMQ prescription services database.

4.4.7 Covariates

In the hypothesis-generating setting of real-time safety surveillance, where it is not yet known which AE will occur, control of confounding can only be made for a restricted number of covariates which tend to be universal for all drug-AE associations, i.e. age and gender. Unlike pharmacoepidemiologic studies which are etiological and aim at testing hypotheses, it is not possible to control for risk factors for the AE (given that the AE is not yet known). Consequently, like previous published studies, age group and gender were the two main covariates.

Confounders that were considered for all analyses consisted of age group and gender. Stratification was used to control for these sources of confounding.

Prescription channelling [112] refers to the selective prescription groups of patients who have a certain susceptibility or specific pre-existing morbidity, where it consists of self-selection or prescribers' preference. For example, medications with the same indication that are introduced on the market at different times, and thus in different competitive situations, may be channelled to different groups of patients. This channelling of a medication may lead to what would appear to be an increased risk of AE associated with a given drug, when in fact treated patients are already at greater risk [113, 114].. There is evidence that for diseases

with a stepped-care approach, the drug history of patients, as available from some databases, can show channeling of drugs to patients with markers of relatively severe disease [112].

One way of controlling for prescription channelling is by considering patient co-morbidity or overall health status. Overall health status is often recognized as an important confounder in pharmacoepidemiologic studies and may therefore be associated with the prescription channelling. Overall health status is therefore not specific to a given drug-AE pair; rather it can be considered as universal and hence, would be appropriate to consider in a surveillance study where it is not possible to control a priori for confounders such as other risk factors for the AE, given that said AE is not yet known. Overall health status is assessed using claims databases, either through prescription or medical services data. Several methods have been published in the literature, and given the nature of the RAMQ databases, the von Korff Chronic Disease Score (CDS) was retained. The CDS is derived from the drugs a patient is using over a one-year period and has been found to be a good predictor of death in the following year [115]. There is evidence that for diseases with a stepped-care approach, the drug history of patients, as available from some databases, can show channeling of drugs to patients with markers of relatively severe disease [112]. von Korff et al developed the CDS composition, where drugs were assigned scores (0 to 5) and such that the CDS would i) increase with the number of chronic diseases but not if drugs of the same class were used; ii) increase as the treatment regimen became more complex; iii) allocate a higher score to more severe diseases and iv) measure medications used for the diseases (as opposed to the symptoms) [115]. The CDS has been adapted and calibrated by (Béland et al. [116]) to reflect diseases not previously considered by von Korff et al, such as

anxiety and depression. It was also updated to include new drugs and new classes of drugs newly available in Quebec over the past decade. Some of the drugs and corresponding weights of the CDS are as follows: Diuretics-1; Statins-1; Cardiovascular drugs (one class-3; two classes-4; three classes-5) etc. Based on the distribution of scores obtained for members of the source population, the following database categories were created: 0; > 0-5; > 5 - 10, >10). The CDS is a method to assess patient overall health status through the summarization of prescription drugs; hence, it is not specific to a given drug-AE association and may be used systematically for all drug comparisons. While previous studies on signal detection controlled for age and sex only, CDS was also an adjustment variable in this study with the premise that it would be an improvement over existing analytic methods of signal detection.

4.4.8 Statistical analyses

The Poisson-based Maximised Sequential Probability Ratio Test (MaxSPRT), described in section 3.1.2.2 (Denominator-based methods) of the literature review, was used as the data mining algorithm.

An exposure denominator that takes into account both the number of exposed patients as well as their length of exposure, i.e. person–time, was used. Exposed and unexposed person-time were calculated using units of patient-months. Exposed person-time began on the day after commencing treatment with the drug, and continued until the end of the last dispensed prescription plus an additional 14 days so as to account for the residual risk period. Exposure gaps of 14 days or less were considered as continued exposure since the

majority of claims in Quebec are for 30 days. A gap of one half of the days last supplied was used as a cut-off in order to account for non-persistence [117]. Hence, all gaps exceeding one half of days last supplied was considered to be discontinuation. Unexposed person-time was quantified as patient-time with no exposure to the drug of interest.

At each monthly time point, the number of expected events in the treatment group was calculated based on the observed risk of the event in the parallel comparison group i.e.

Cumulative number of AEs in reference group	X	Cumulative pt-exposure of treatment

Using monthly data, the LLR test statistic comparing observed counts to expected counts, was calculated at time t of each drug-event pair. A potential AE signal was generated if the LLR exceeded a pre-defined critical value. A different critical value was established for each drug-AE pair using pre-calculated computer-based simulations provided by Kulldorff et al [57]. MaxSPRT critical values are calculated such that the null is rejected when the LLR reaches an upper limit and accepted when the observation has been ongoing for a pre-determined length of time. It is, defined in terms of the expected number of events accumulated under the null hypothesis (H_0) Kulldorff et al provide a table of values within their study, which indicates the upper bounds used for the rejection of the $H_0$for various denominations of alpha levels, and expected number of events under the H_0. These values can be employed by subsequent users of the MaxSPRT method.

For this study, critical values were set up such that the alpha level was 0.05; the minimum number of events under the H_0 was five (based on evidence that the minimum number of AEs required to uncover a signal for a rare AE is between three and five [88]), and the maximum length of follow-up was 120 months i.e. the available study period in the database (1st January 2000-31st December 2009). The time to detection of the potential risk (signal) using this method was compared to that of the posting of the actual safety communication by Health Canada (dates provided in Table V of section 4.4.2 "Selection of drug-adverse event pairs").

4.4.9 Statistical power

Applying this method in real time, the sample size of the study would not be known until analysis has actually begun. Furthermore, the sample size would also be limited by the size of the database, which was the case with the current study. Consequently, the statistical power of the study to detect drug-AE associations was determined after analyses of each pair with the use of a table of pre-determined values provided by Kulldorff et al [57] (Table II). Kulldorff et al calculated various values of power based on: the type I error, the upper length of surveillance, and the true RR of the AE of interest. Tables IX and X in the "Results" section display the statistical power calculated for each of the analyses.

4.4.10 Control of biases

Because the hazard function that describes the change in risk over time after treatment initiation is rarely constant over time, it is necessary to account for duration of drug use. In

many instances, risk of AE increases with time immediately after treatment initiation and decreases thereafter. This phenomenon is referred to the "depletion of susceptibles" effect whereby individuals who did not experience symptoms of the AEs during the period at highest risk will likely not experience it at later stages [119]. As shown by Moride and Abenhaim (1994)[111], failure to take into consideration time since treatment onset may introduce a bias in the measure of association between a drug and an AE, especially when comparing the risk associated with various products. Thus, continuing follow-up of a drug in one patient for a long period of time could reduce the strength of a signal, as less AEs would be reported as time lapses. In order to eliminate this source of bias, we have used a "new user" design in the definition of the cohorts [118]. All patients exposed to the drug of interest or to the comparator had not received any prescription for this given drug in the previous six months.

Prevalence bias is a type of selection bias that may occur in studies when prevalent cases rather than new cases of a condition are selected. Prevalent cases are patients who have survived with their AEs. Hence, it is not known whether the drug is a risk factor for the occurrence of the AE, or whether it is a prognostic factors in patients who have the AE. Previous studies have excluded patients with a history of AE during the 6 months prior to the occurrence of the current AE [63]. It was decided not to exclude on such basis in the current study given that in a true signal detection setting, one would not know which AE will occur; hence it is not possible to exclude on such history. However, controlling for overall health status would allow control for prevalence bias as well.

4.4.11 Sensitivity analyses

Sensitivity analyses were performed in order to test the robustness of the method, and the effect of controlling for different combinations of confounders

Time windows for follow-up

In addition to the default follow-up time of 3 months, additional time windows of 6 months and 12 months were also analysed for all drug-AE pairs, in order to determine the effect of controlling for depletion of susceptibles effect as described in section "Control of bias'" 4.4.10 above.

Age, sex

Age: As described in section 4.4.7"Covariates" above, to control for age (five-year intervals), subgroup analyses were applied to all drug-AE pairs in a similar manner to a standardised mortality ratio (SMR) process (i.e. a method whereby expected numbers are calculated per group (i.e. age or gender) and then totalled. With the SMR, the numbers of deaths that were actually observed in the population are also calculated and totalled. The ratio of the total number of deaths observed, to the total number of deaths expected is then calculated subsequently) [120].

Following the formula indicated in the "Statistical analysis" section above, separate expected AE counts were calculated for each of the subgroups on a monthly basis, by first calculating risk values for each, and then multiplying the risk by the monthly cumulative patient exposure for each of the same. These expected event counts were then averaged for the entire treatment cohort at the monthly level, before applying the LLR test.

Sex: Subgroup analyses based on sex were also applied to all drug-event pairs with the exception of two pairs studied only in female patients: the "pioglitazone-" and "rosiglitazone-increased fractures" pairs. A similar method to that performed for the age adjustment was applied to the subgroups of "male" and "female" subjects. Given that the RAMQ provided age groups in 5 year intervals as opposed to exact birth dates, only a crude control could be achieved, which is a limitation of the study.

Age, sex, overall health status

After adjustments on age and sex, the effect of overall health status was also analysed for the rosiglitazone-acute MI drug-AE pair by including the subgroup of CDS. CDS is described in further detail in section 4.4.7 "Covariates"above. For each patient of the cohort, CDS was calculated based on the drugs used during the year prior to initiation of treatment use. Scores were subsequently stratified into subgroups which were determined based on the observed distributions of CDS in the study population: (0; > 0- 5; > 5 - 10, >10).

Include versus exclude history of MI

The initial analysis of the drug-AE pairs did not control for or exclude prior occurrences of the AE of interest. In order to control for prevalence bias, where a medication appears to cause an AE in patients already suffering from the AE, patients who had previously exhibited the event of acute MI within the 6 months prior to incident exposure within the rosiglitazone-acute MI pair were excluded from the analysis.

4.4.12 Results

Table VII. Baseline Characteristics of study cohort

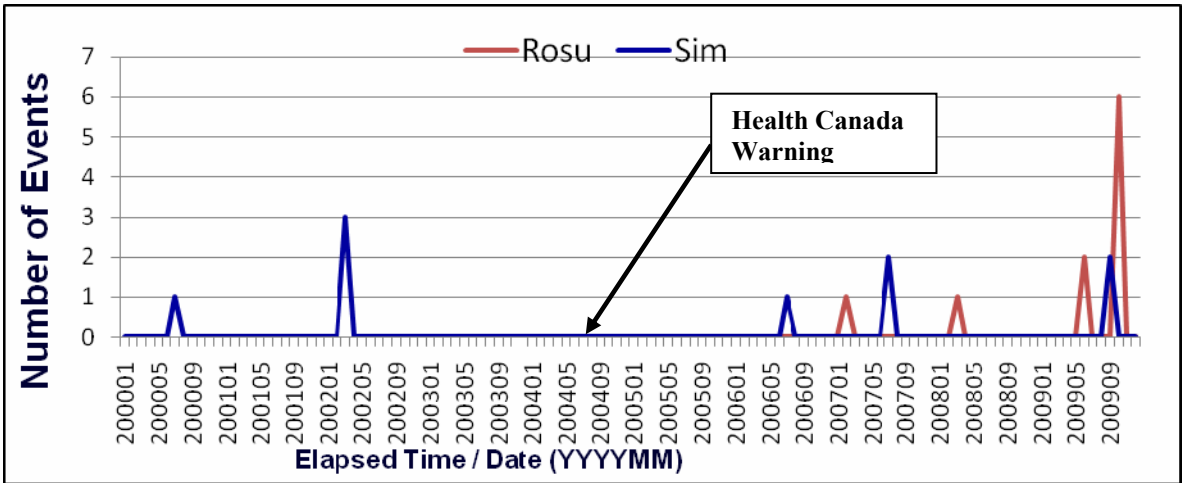
		N	%
Total		87389	100
Gender			
	Female	49718	56.89
	Male	37671	43.11
Age at cohort entry			
	66-69y	49002	56.07
	70-74	15843	18.13
	75-79	11379	13.02
	80-84	6413	7.34
	85 and over	4739	5.42
	Not Indicated	13	0.01

Table I shows the baseline characteristics of the study cohort. A large majority of the population were between the ages of 66 and 69.

Data mining results: Known drug-AE pairs

Rosuvastatin-rhabdomyolysis ("other statins" reference): Figure II displays the background rates of rhabdomyolysis within users of simvastatin and rosuvastatin. Due to the few number of AEs, the database appears to be too small for application of the MaxSPRT method. Instead, a simple Poisson method was applied to determine where an unexpectedly high amount of AEs were observed in rosuvastatin users, as compared to users of "other statins".

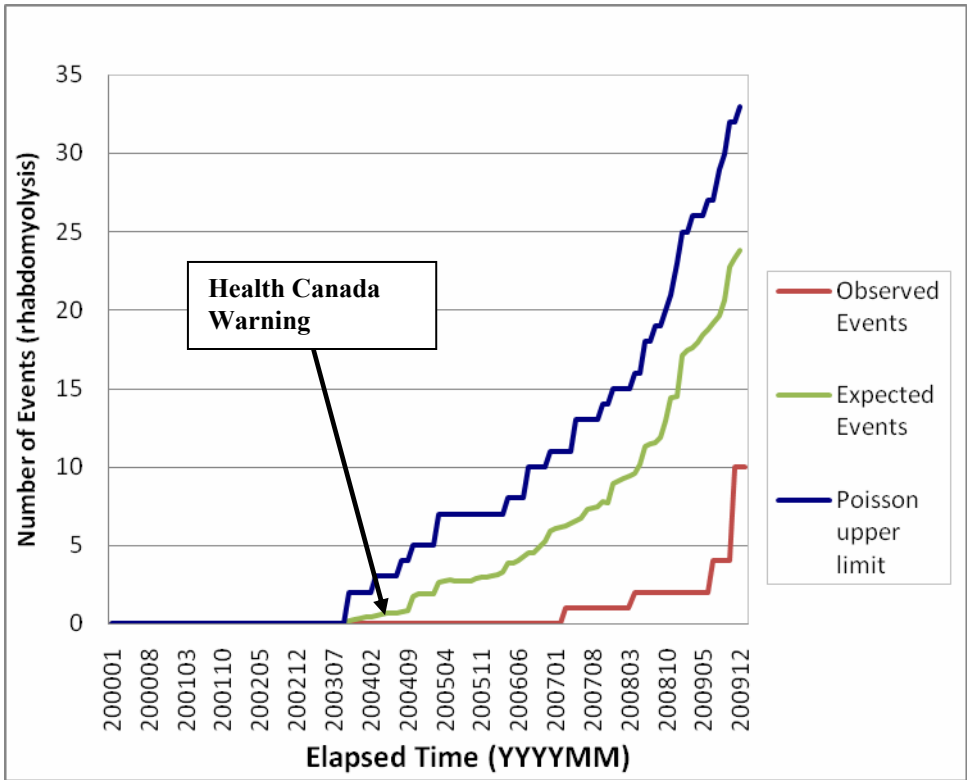
Figure II. Background rates of rhabdomyolysis during study group in statin groups within RAMQ Database



The Poisson method also did not show a potential signal in the pair as can be seen below in Figure III: The observed number of events of rhabdomyolysis within the rosuvastatin group remained lower than the expected number of events (based on reference groups of

simvastatin and atorvastatin). It also remained far lower than the upper boundary that would have indicated a signal as per the Poisson method.

Figure III. Rosuvastatin-rhabdomyolysis poisson data results – three month follow-up



Rosiglitazone-acute myocardial infarction (metformin reference):The three-month time window shows the detection of a safety issue at 107 months from product launch. The six-month time window shows a signal at 108 months, and the 12-month time window does not show a signal.

Rosiglitazone-increased fractures in female patients (metformin reference):There was no potential signal observed with the rosiglitazone-increased fractures pair with any of the

follow-up time windows or adjustments. There was no significant increased risk when comparing observed to expected counts. The power of the analyses was less than 0.2.

Pioglitazone-increased fractures in female patients (metformin reference):There was no potential signal observed with the rosiglitazone-increased fractures pair with any of the follow-up time windows or adjustments. There was no significant increased risk when comparing observed to expected counts. The power of the analyses was less than 0.2

Data mining results: Negative controls

***Alendronate – acute hepatitis (atenolol reference) and Amitriptyline – increased fractures (metoprolol reference*)**:

Table VIII below shows that neither of the negative-control pairs produced any potential signal throughout any of the follow-up time periods. These results were not affected by adjustments on age and sex. However, using the six-month follow-up period, there was a peak that came close, in the alendronate-acute hepatitis group at January of 2003.

Table VIII below also provides an overall summary of the unadjusted MaxSPRT data mining results for the remaining drug-AE pairs. The only drug-AE pair that shows a potential signal is the rosiglitazone-acute MI pair, during the three-month and six-month follow-up time windows. This study had a power of 0.5 to 0.6. The other known-drug-AE pairs did not show a potential signal, nor did the negative-control pairs. However the power for all of these remaining analyses was between 0.1 and 0.2. Each drug-AE pair is discussed in further detail below.

Table VIII. Unadjusted results of MaxSPRT data mining method applied to drug-AE pairs

Drug–AE Pair	Follow-up Time Period	Cumul. number of person months in cohort	Number of person-months in cohort at signal	Maximum Expected Number of Events under Ho	Expected Number of Events under Ho at signal	LLR Critical Value ($p < 0.05$)	Date of Health Canada Warning	Number of events observed at signal	Month and Year Signal Detected	Number of months to signal	Study Power
rosiglitazone – acute myocardial infarction (vs. metformin)	3 months	52906	51704	92	89	3.95	Nov 2007	118	Oct 2009	107	0.252 to 0.869 (Interpol-0.458) (RR=1.3)
	6 months	90941	89782	118	118	3.99	Nov 2007	151	Nov 2009	108	0.366 to 0.997 (Interpol - 0.567) - (RR=1.3)
	12 months	91059	N/A	136	N/A	4.03	Nov 2007	N/A (max=153)	No signal	No signal	0.421 to 0.502 (RR=1.1)
rosiglitazone-Increased fractures in female patients (vs. metformin)	3 months	3064	N/A	15	N/A	3.57	Feb 2007	N/A (max =12)	No signal	No signal	Less than 0.122
	6 months	5452	N/A	22	N/A	3.68	Feb 2007	N/A (max =14)	No signal	No signal	Less than 0.122
	12 months	9849	N/A	36	N/A	3.78	Feb 2007	N/A (max =23)	No signal	No signal	Less than 0.195
pioglitazone Increased fractures in	3 months	1731	N/A	6	N/A	3.35	Apr 2007	N/A (max =7)	No signal	No signal	Less than 0.091

female patients (vs. metformin)											
	6 months	2953	N/A	9	N/A	3.47	Apr 2007	N/A (max =10)	No signal	No signal	Less than 0.106
	12 months	5109	N/A	14	N/A	3.57	Apr 2007	N/A (max =16)	No signal	No signal	Less than 0.122
amitriptyline-Increased fractures in female patients (vs. metoprolol)	3 months	11173	N/A	51	N/A	3.35	N/A	N/A (max =39)	No signal	No signal	Less than 0.091
	6 months	15846	N/A	67	N/A	3.47	N/A	N/A (max =63)	No signal	No signal	Less than 0.106
	12 months	24095	N/A	86	N/A	3.57	N/A	N/A (max=100)	No signal	No signal	Less than 0.122
alendronate - acute hepatitis (vs. atenolol)	3 months	26411	N/A	13	N/A	3.57	N/A	N/A (max =17)	No signal	No signal	0.112 to 0.318 (Interpol-0.182)
	6 months	43166	N/A	18	N/A	3.63	N/A	N/A (max =25)	No signal	No signal	0.112 to 0.318 (Interpol-0.182)
	12 months	77046	N/A	22	N/A	3.68	N/A	N/A (max =32)	No signal	No signal	0.136 to 0.451 (Interpol-0.241)

Effect of adjustments on age and sex- Rosiglitazone-acute myocardial infarction case study (metformin reference):VIII below displays a direct comparison of the three-month and six-month follow-up time windows within the "rosiglitazone-acute MI" pair. The three-month time window shows the detection of a safety issue at 107 months from product launch. Adjusting these results on age and sex improves the time to detection to 93 months. The six month time window initially shows a potential signal at 108 months. The age & sex adjustment improved it to 93 months. All with powers between 0.5 and 0.6.

Effect of adjustments on age, sex and CDS - Rosiglitazone-acute myocardial infarction case study (metformin reference):

Cumulative adjustments of the CDS in addition to age and gender at the three-month interval allow for an even earlier detection of a potential signal at 83 months in September 2007, two months before Health Canada's issuance of the safety warning. The CDS adjustments at the six-month interval (combined with age and gender) led to detection at 61 months in November 2005, 24 months before Health Canada's warning.

Effect of exclusion of previous AE occurrence - Rosiglitazone-acute myocardial infarction case study

At the three-month time window, excluding individuals with prior experience of acute MI within six months prior to exposure to the drug of interest, further sped up the detection of a potential signal to 29 months, with a power between 0.5 and 0.6. However, at the six-month time window, excluding prior AE's within six months pre-exposure leads to no detection at the six-month time window, involving a power of just 0.2.

Table IX MaxSPRT data mining results of rosiglitazone – acute myocardial infarction pair using three-month and Six-month follow-up time periods

Follow-up Time Period	Adjustment	LLR Critical Value ($p < 0.05$)	Cumul Number of person – months in cohort	Number of person-months in cohort at signal	Maximum Expected # of Events under Ho	Expected # of events under Ho at signal	Date of Health Canada Warning	Month and Year Signal Detected	# of months to signal	Number of events observed at signal	Power of study	Interpolated Power Calculation
3 months	None	3.95	52906	51704	92	89	Nov 2007	Oct 2009	107	118	0.252 to 0.869 (RR=1.3)	0.458
	Age & Sex	3.92	52906	42763	84	68	Nov 2007	August 2008	93	94	0.309 to 0.904 (RR=1.3)	0.507
	Age Sex & CDS	3.86	52906	36060	71	50	Nov 2007	Sep 2007	83	72	0.252 to 0.869 (RR=1.3)	0.458
	Age, Sex, CDS & Exclusion of MI in previous 6 months	3.72	52788	4532	30	5	Nov 2007	Mar 2003	29	13	0.599 to 0.983 (RR=1.6)	0.599
6 months	None	3.99	90941	89782	118	118	Nov 2007	Nov 2009	108	151	0.366 to 0.997 (RR=1.3)	0.576
	Age & Sex	3.96	90941	72573	108	90	Nov 2007	August 2008	93	119	0.366 to 0.997 (RR=1.3)	0.576

	Age Sex & CDS	3.92	90941	38175	91	42	Nov 2007	Nov 2005	61	65	0.309 to 0.944 (RR=1.2)	0.507
	Age, Sex, CDS & AE excl in previous 6 months	3.83	90941	N/A	51	N/A	Nov 2007	No signal	No signal	N/A (max=58)	0.223 (RR=1.2)	0.223

CDS = Chronic Disease Score

Figure IV below displays the number of counts of the observed vs. expected AEs; as well as the signal detection graph, for the three-month follow-up of rosiglitazone-acute MI pair adjusted for age, sex, and CDS. Although the potential signal from the data mining method was observed at 83 months, the imbalance in observed vs. expected AE counts is seen to commence as of 56 months in Jun 2005 (39 events vs. 34 events).

Figure IV. Rosiglitazone-acute MI data mining results – three month follow-up adjusted for age, sex and overall health status (CDS)

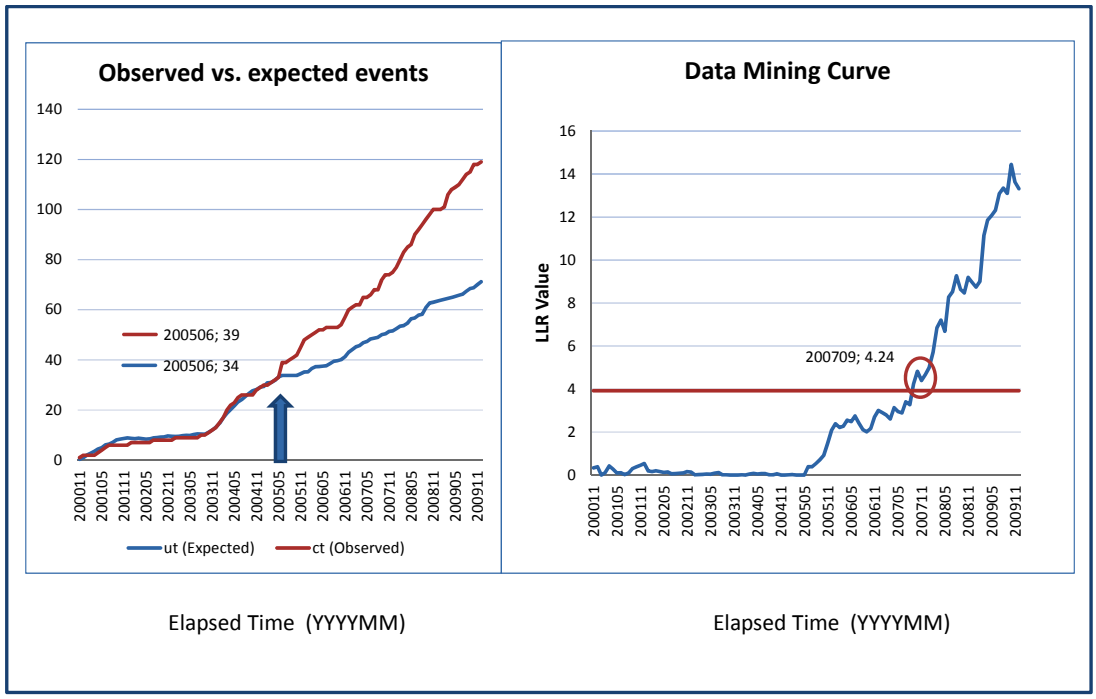
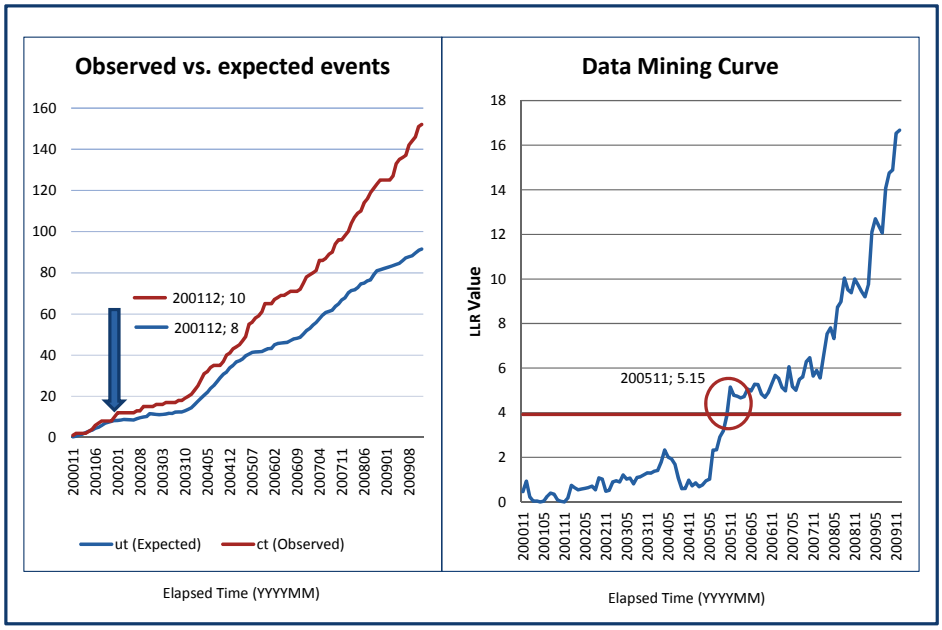


Figure V below displays the number of counts of the observed vs. expected AEs; as well as the signal detection graph, for the six-month follow-up of rosiglitazone-acute MI pair adjusted for age, sex, and CDS. Although the potential signal from the data mining method was observed at 61 months, the imbalance in observed vs. expected AE counts is seen to begin as of 13 months in Dec 2001 (10 events vs. 8 events)

Figure V. Rosiglitazone-acute MI data mining results – six month follow-up adjusted for age, sex and overall health status (CDS)



4.4.13 Discussion

4.4.13.1 Strengths

This study is the first data mining study for signal detection to be applied to a Canadian health claims database. Literature searches have revealed only one previous study applied to a Canadian database. This was however the Health Canada SR database [73], and compared the denominator-independent methodologies of PRR, ROR, the Chi-square statistics methods, and the Du Mouchel method to calculate possible signals. This is in stark contrast to our method which used an administrative claims database, and a denominator-based method to determine the presence of potential signals. Thus to our

knowledge, this is the first study to attempt detection of potential safety signals through a Canadian claims database, and using a denominator-based method. The use of the RAMQ database provided strengths such as a large sample size and longitudinal data that is extremely comprehensive for the elderly population of the province of Quebec (97% covered in public drug program). Furthermore the use of this database avoids common data mining and signal detection challenges of underreporting and reporting bias that occur in the SR databases, and virtually eliminates any potential for selection bias. Because of the diversity and completeness of data within this database, the potential for future signal detection activities of verification and confirmation through pharmacoepidemiologic studies is also quite promising. This study also accounts for the depletion of susceptibles in a data mining study by varying the length of follow-up for each of the drug-AE pairs in order to observe variations on the strength and time to detection of potential signals. This is a characteristic that other studies have not factored in the past. Finally, the calculation of expected events in this study is based on a parallel reference group. This also is a unique approach taken in this study as the previous Brown et al studies [31,63] calculated the events based on the assumption that the comparator group contained at least some historical data. For this reason, a constant risk value of the comparator group had been applied to prior studies [31,63]. However this study instead uses a variable risk that is calculated at each monthly time point, in order to determine the expected counts for that particular month. This is deemed to be more pragmatic than the historical approach, and would also account for seasonal changes, as well as changes in the product's usage profile over time.

4.4.13.2 Weaknesses

Size of database

The size of the database that the RAMQ provided for the analysis was a relatively small proportion (approximately 11%) of the RAMQ database (n=87389). This number is rather small in comparison to other databases used in prior data mining studies (Brown et al n= approx. 8million; Choi et al n=1,093,262; Coloma et al n=59,929,690). It is presumed that the effects of this limited database size on this study were the low power, and inability to detect signals in 2 out of four of the case studies, i.e. the rosiglitazone and pioglitazone-increased fractures pairs. The power of the negative-control pairs was also very small, leading to some reservations in the interpretation of the specificity of the tool.

Age group within database

In Quebec, all persons 65 years or older are eligible for coverage under the RAMQ services[121], thus it contains 97% of the elderly population for both medical services and prescription data, and is ideal for post-marketing studies of this group. This is beneficial for signal detection activities in this particular group, which is one that has been targeted by the FDA and EMA for risk management activities. The medical services database also includes more than 99% of the claims for the remainder of the population of Quebec [122], however not all individuals are covered by the prescription services which contains only 55% of the total population for medication exposure data [123, 124]. This limits its applicability to signal detection in groups outside of the elderly population as i) the sample size provided may be too small for analysis, and ii) the generalizability of the results to the overall population of Quebec may be questionable.

Potential inaccuracy of ICD-9 codes

As mentioned in "Health Claims Databases" section 3.1.3.3, the reliability of the ICD-9 diagnostic codes reported by the HCPs may be questionable as validation is not required for reimbursement. Although there are studies which indicate that the specificity of ICD-9 codes reported by Physicians for reimbursement, including those for cardiovascular risk factors, are usually 95% or greater [109, 125], there were no studies located concerning the validation of the codes for acute MI in Canada. Furthermore, there is a general lack of Canadian validation of the ICD-9 codes used in this study overall. In general, use of the incorrect ICD-9 code, or misdiagnoses could result in a misclassification of the events, and possibly many events being omitted from the analysis. This in turn could reduce the size of the signal and increase the time to detection of the signal as well. Thus the risk of inaccuracy of the ICD-9 codes used in this study could be contributing to the lack of a signal, and low power observed with some of the case studies. In addition, in some cases the misclassification of the event could lead to the event's counts being so rare that too few events are identified in order to apply analyses at all. This is believed to be one of the causes of the missed signal in the rosuvastatin-rhabdomyolysis case study as described further below.

Calculation of expected events Additional weaknesses observed throughout this process include the inability to detect very rare AEs such as rhabdomyolysis using this method. However, application of the Poisson method also did not produce a potential signal. This could in part be due to the use of inaccurate ICD-9 codes, as the precise code for rhabdomyolysis is a five-digit code, however the RAMQ database only contains up to four digits for ICD-9 codes. It could also be due to the database not being large enough (14,583

rosuvastatin users for the entire 10-year timer period), however, these results are consistent with a study by Choi et al that did not pick up rhabdomyolysis as an AE signal when analyzing AEs of rosuvastatin in a Health Claims database in China [30] which consisted of 96, 236 users of rosuvastatin over a one-year period. On the other hand, Szarfman et al [49], and Brown et al [63] did determine a signal using the cerivastatin -rhabdomyolysis case study, and a data mining algorithm. Cerivastatin however is a drug that was approved by the CM of Quebec in 1997, three years before the inclusion dates of our sample, making it an inadequate case study for our method. Cerivastatin was also voluntarily withdrawn from the world market in 2001 due to its association with rhabdomyolysis and death, implying that it possibly had a much larger RR than our case study of rosuvastatin-rhabdomyolysis. Because of the extremely rare nature of the AE of rhabdomyolysis among users of "other statins", it is not possible to use this particular automated methodology and this particular database to identify this sort of AE. This feature indicates that it is necessary to continue traditional qualitative or non-automated signal detection methodology, and that the automated data mining methods should be used as an *adjunct* to traditional qualitative methods [28,38]. This is a conclusion consistent with general consensus of data mining methodology. Furthermore, there is a general lack of Canadian validation of the ICD-9 codes used in the analyses which would affect the accuracy of the results.

Only a basic, less refined control of the covariable of "age" was achieved due to the fact that the RAMQ database provides age groups in 5 year intervals rather than the exact birth dates.

As with most pharmacoepidemiologic studies, there is the possibility of the presence of unmeasured confounders, that cannot be adjusted for. This could distort the results of the study.

Feasibility of using this method depends on the availability of data on a quarterly basis. Given the current situation in Quebec where delays for RAMQ data extraction are very large, the administrative system is not set up for this. Furthermore, drug dispensings become available in the RAMQ database only when the drug is reimbursed by the public drug plan. In practice, delays for inclusion in the drug formulary are increasing which therefore hampers the ability to conduct data mining immediately following product launch. In this demonstration study, the analytical methods were developed and the performance of the tool was assessed. Currently, limitations in the timeliness of the availability of the RAMQ database is a major barrier to the implementation of data mining for drug safety signal detection in Canada.

4.4.13.3 Controlling for confounding and biases

The main limitation of data mining is that the ability to detect safety signals is offset by a very large number of false-positive signals, each requiring further investigations. In order to reduce the number of false-positive signals obtained during the data mining process, confounding factors are controlled for. A potential signal was observed with the unadjusted rosiglitazone-acute MI case study. This is in fact consistent with the results of the Motola et al study [126] which showed disproportionality with cardiovascular ADRs among the rosiglitazone study group. In addition, subgroup analysis of our study data by age and

gender had a profound effect, causing the potential signal to be detected around one year earlier in the rosiglitazone- acute MI group (See Table IX above).

As a means to control confounding by overall health status, the CDS was applied to the "rosiglitazone- acute MI drug-AE pair. The CDS was described in detail in section 4.4.7 "Covariates". It is an indicator of overall health status of a patient developed by von Korff and is acquired based on the drugs a patient is using over a one-year period[115]. It is believed that this is a straightforward method that can be applied at various levels of research. Nonetheless, calculating the CDS is still a fairly tedious procedure and it is suggested that it only be applied to drug-AE pairs showing the most potential effect as was done in this study where it was applied only to the rosiglitazone-myocardial infarction pair. Many previous studies have not included any adjustments or attempts to control for confounding [47,89,95,]. Other studies methods to control for confounding have been primarily limited to stratification on demographics such as age, sex, and gender [49,50]. Choi et al [30] included only elderly patients in order to control for confounding by age, and Poluzzi et al controlled for prevalence bias by excluding individuals who previously exhibited the AE of interest. They also controlled for concomitant medications by conducting qualitative case-by-case analyses of the spontaneous reports included in the study. There have also been discussions on the possibility of using a form of a Propensity Score known as the High Dimensional Propensity Score (HDPS). This is a multi-step process that encompasses covariates of two main categories i. Demographics (age, sex, calendar time, race) ii. Candidate Empirical Covariates (outpatient diagnostic ICD codes; inpatient procedure codes, and drugs dispensed). The prevalence, recurrence, and priority of these codes are also assessed in order to determine the most adequate ones to include in the multivariate

logistic regression formula that would define the HDPS [127]. This method is indeed more advanced than the application of CDS used for our study; however HDPS construction is quite complex and believed to require much more resources than the CDS.

4.4.13.4 Effect of depletion of susceptibles

As discussed in the methods section 4.4.10 "Control of biases", the phenomenon of depletion of susceptibles [111] is a situation whereby patients who remain on drugs for a prolonged period of time, are those who can tolerate them, while those who are susceptible to side effects select themselves out of the population at risk. Thus, continuing follow-up of a drug in one patient for a long period of time could reduce the strength of a signal. Accounting for the depletion of susceptibles in a data mining study is not a characteristic that other studies have factored in the past.

From Table VII, one can note that for the non-adjusted rosiglitazone-acute MI data, although the power for the six-month intervals is higher than that of the three-month interval (0.6 vs. 0.5), it is the three-month interval that gives a stronger and earlier signal. We believe that this exemplifies the effect of the depletion of susceptibles phenomenon. The meta-analysis conducted by Nissen and Wolski[128, 129] which initially showed the increased risk of acute MI in rosiglitazone users, did not have access to individual patient files and could not determine the actual time to onset of the acute MI. All clinical trials included in the analysis were of duration of at least 24 weeks (6 months). Consequently, the theory of depletion of susceptibles with regards to the 3-month time interval is difficult to support. However, Table VI of our signal detection study also shows us that there is no

potential signal observed with the 12-month time window of unadjusted results, although the 6month time window did produce a signal This is also believed to be attributable to a depletion of susceptibles effect masking the signal in the signal detection study for the longer period of 12 months. This is consistent with the results of the meta-analysis by Nissen and Wolski where trials of less than 12 months' duration showed a higher risk of acute MI (OR, 1.76 (95% CI, 0.93-3.33) than trials of 12 months and longer (OR, 1.22 (95% CI, 0.95-1.57). The RR for the 6 month and 12 month time periods (1.3 and 1.1. respectively) were slightly lower than the ORs of Nissen and Wolski although they do fit in the 95% confidence intervals. These risk estimates demonstrate that our calculation of expected events is in line with the literature and it is expected that it may be difficult to detect a signal at the 12month time point given that the risk is lower for that length of follow-up. We believe the reason for the lower risk in the longer time period is the fact that those who are susceptible to experiencing AEs select themselves out of the population at risk. E.g. in the DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) trial, some common reasons for stopping rosiglitazone and placebo were: edema (439 [4.8%] in the rosiglitazone group and 41 [1.6%]) in the placebo group, physician's advice (50 [1.9%] and 39 [1.5%]), and weight gain (50 [1.9%] and 15 [0.6%], indicating that susceptibility to AEs plays a large role in decisions to discontinue therapy [130].

It is also possible that the reduced ability to detect a signal in the 3month time period (adjusted for age, sex and CDS) is due to the fact that the time to onset of MI could, on average be more than 3 months. Thus the follow-up period may be too short to detect a substantial signal at an earlier time point. This further supports the use of varying follow-up

time periods during signal detection processes in order to increase potential for signal detection.

4.4.13.5 Exclusion of previous AE occurrences

The exclusion of previous occurrences of acute MI also allowed for a signal in the 3-month period, but none in the 6-month period. It is believed that the exclusion of prior acute MI events reduced the power of the 6 month time period such that the AE could not be detected in this group (0.223 for 6months vs. 0.599 for 3months). This is believed to be the main reason that the 3month time window has a better signal at this point. This exclusion of previous AEs also shows evidence that the drug could be playing a larger role at exacerbating previous events of acute MI as well as causing new events.

The use of comparator drugs with the same indication as the study drugs, are expected to control for indication bias. Survivor bias is also controlled for due to the analysis beginning at the start date from the drug's reimbursement. Finally, misclassification is also addressed due to the use of incident exposure, and exposed vs. unexposed person-time denominator in the calculations.

4.4.13.6 Challenges encountered in the study

No safety risk was observed with the remaining two known drug-AE pairs of rosiglitazone and pioglitazone-increased fractures in female patients. However in a prior study, Motola et al were able to demonstrate that pioglitazone showed significant RORs compared to other anti-diabetic drugs within the FDA-AERS database [126]. Our inability to detect a signal

could be due to the low statistical power noted with the analyses of these two pairs (both approximately 0.1), implying that the database may in fact be too small for analysis of certain drugs with either low exposure rates or low occurrence of the AEs. However, it is also important to note that the data mining and signal detecting processes are hypothesis-generating methods which would require further analyses (e.g. traditional pharmacoepidemiologic studies) in order to confirm that a signal or true safety risk actually does exist. Thus having a low power is more common among these studies than others. .

Although the negative control drug-AE pairs did not produce signals, the alendronate-hepatitis pair did come close at January of 2003 using the six- month follow-up time period. This peak could in part be due to the surge in exposure that occurred between Dec 2002 and October 2003. Furthermore, the power of the data mining methods of these two negative-control drug-AE pairs also appears to be relatively low (0.1 and 0.2 respectively).

With the unadjusted rosiglitazone-acute MI pair results there appears to be a question of the possible existence of notoriety bias. i.e. after the issuance of the warning, the reporting of acute MI increased thus resulting in a signal. However because the actual figures of observed vs. expected events (Figure IV for 3month period and Figure V for the 6 month time period) show the imbalance of events beginning as of June 2005 and December 2001 respectively, this is unlikely to be the case.

Accounting for time to onset of AE, or residual time periods after exposure, is an aspect that would be difficult to include in future application of the methodology given that in a real world prospective case scenario, the AE of interest is unknown. Thus, controlling for

such factors is not possible. As such, the study did not take into effect a lag time to onset of AE, and used a standard residual period of 14 days. No other studies attempting either of these facets were located during the literature review. However for future use, if a particular and specific AE has been defined for analysis, then this may be possible. The UMC uses an algorithm to filter what AEs should be analysed, prioritizing those that are: serious and new events; of increasing reporting frequency; clinically of special interest due to their typical association with drugs (e.g. rhabdomyolysis, agranulocytosis and Stevens-Johnson syndrome) and; 'international signals' that are reported from multiple countries [131,132]. Consequently if an organization wishes to routinely study AEs such as those listed above, then further limiting the number of false positive signals by defining time to onset of AE, and/ or residual time periods after exposure may be a viable option.

4.4.13.7 Future perspectives

Using less severe symptoms as proxies for diseases that are difficult to diagnose, or very rare AEs may be a solution to data mining of very rare events, (e.g. rhabdomyolysis: proxies of less severe symptoms such as myopathy, myoglobinuria, myositis, muscle weakness etc.) specifically since ideally one would want to identify the AE before it becomes as severe as rhabdomyolysis. However using proxies could lead to the unwanted effect of additional "background noise" false positive signals, which would make the process more tedious.

Accounting for time to onset of AE, or residual time periods after exposure in order to further reduce the false positive signals is an idea that may be worth exploring in instances where particular AEs have been identified for study.

Use of the database for the next step in signal detection, i.e. verification / confirmation of the signal, is also a potential next step with the RAMQ database because it contains much information on potential confounders such as concomitant medications.

Finally, applying the method to the RAMQ database, in a real-time manner using newly marketed drugs. The potential AEs to be studied could be AEs known to be associated with the class effects of the drug, or mechanism of action, or high-profile AEs. However this would depend on the RAMQ updating the database on a schedule that would allow for this. This would also most likely be limited to medications used in the elderly, since the RAMQ database may not possess a representative number of other groups of the population.

4.4.14 Conclusion

In the context of therapeutic risk management, this study helps us to identify certain gaps in the field of risk detection through the use of statistical methods. The data mining algorithm of MaxSPRT is indeed applicable to the RAMQ database and the database seems to be conducive to quantitative signal detection. This further supports the use of administrative claims databases vs. SR databases for data mining. There are however still limitations with

the size of the database, and thus the power of certain drug-AE pair analyses. Consequently the method may need to be refined for each drug-AE pair individually in order to improve its performance. The sensitivity of the tool was demonstrated with just one of the four known drug-AE pairs through the detection of a safety concern, and the time to detection of the potential signal. The specificity of the tool was also established since none of the negative-control pairs analysed resulted in a potential signal being identified. However the power of each of these analyses could cause some ambiguity with regards to interpretation of the results. The definition of the time window is a crucial element for the ability to detect signals in order to avoid the depletion of susceptibles effect. This is an aspect that future researchers should take into consideration in order to possibly identify signals earlier, and take action at protecting patients much sooner. This tool is expected to be adaptable for use by academic researchers, industry and regulators in order to improve drug safety surveillance in the Canadian population, and serve as a supplement to current methods of qualitative signal detection, helping advance the field of therapeutic risk management

Chapter 5. Review of Risk Minimisation Interventions: Impact of regulatory guidances and drug regulation on risk minimisation interventions in drug safety: a systematic review

5.1 Introduction to risk management and risk minimisation interventions

5.1.1 Risk management

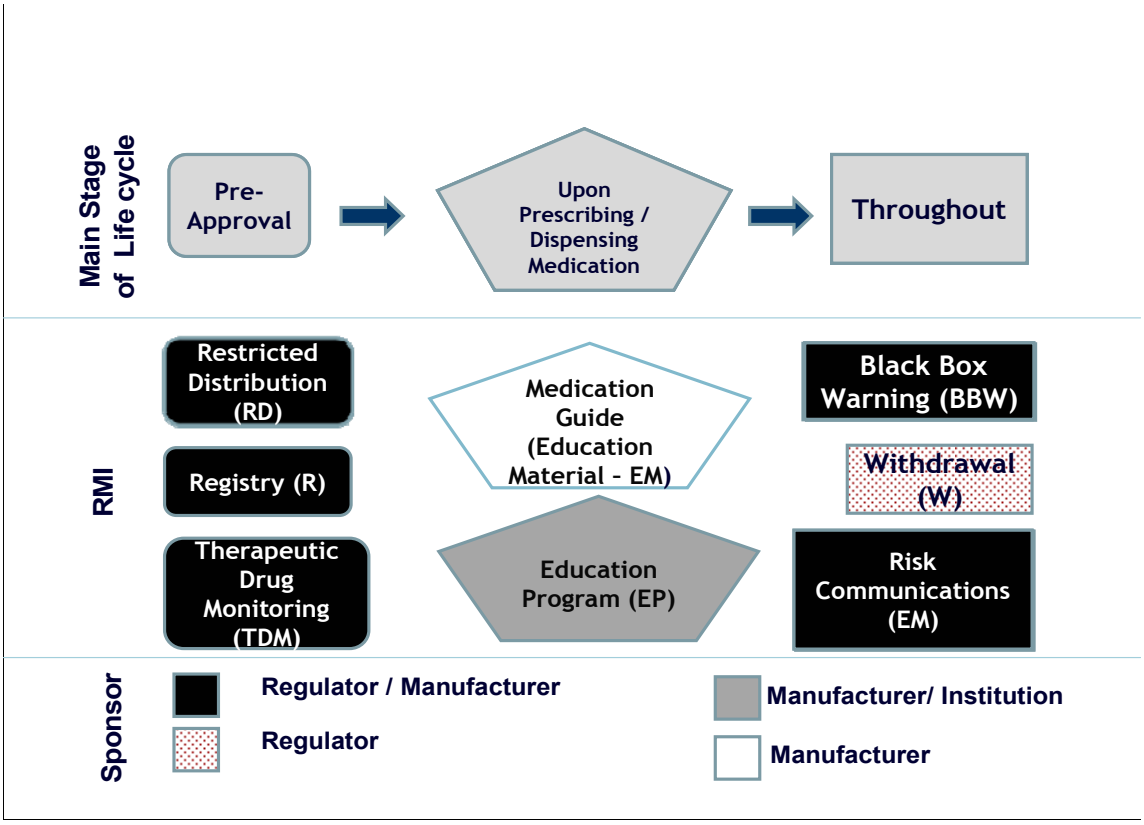
Therapeutic Risk Management is a comprehensive and proactive application of scientifically-based methodologies and involves assessing, communicating, and minimising risk throughout a drug`s life cycle [10]. This field has received growing interest over the past decade as manufacturers and regulatory authorities increasingly seek to prevent the occurrence of adverse events (AEs) associated with pharmaceutical drug products. Risk minimisation interventions (RMIs) used in therapeutic risk management have existed for several decades; however it was not until June 2005 that both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) integrated into their regulations, guidelines concerning Risk Management. Since the publication of these regulatory guidelines an increasing number of risk minimisation/mitigation interventions have been implemented.

5.1.2 Risk minimisation interventions

According to the EMA, a Risk Minimisation system is: a set of activities used to reduce the probability of an adverse reaction occurring or its severity should it occur [9]. RMIs are tools which aim at reducing

the risk of AEs among patients using medications, while preserving their benefits throughout the drug's life cycle [10]. They vary widely and can be specific to country, target audience, and stage of drug's life cycle at which it is implemented such as: marketing authorisation; prescription of drug; dispensing of drug etc. Figure VI shows some RMIs and indicates stages at which they can be implemented. The next section contains descriptions of RMIs.

Figure VI. Examples of RMIs based on main implementation stage of product life cycle



5.1.2.1 Restricted Distribution(RD) is an example of a set of restrictions and conditions implemented during the marketing authorisation process of a drug. RD is generally used in situations where restrictions are imposed on various aspects of access to the drug such as: who can prescribe the

medication; where the product can be dispensed or administered; or the amount of the product that can be dispensed to a patient at a time [133]

5.1.2.2 Therapeutic Drug Monitoring(TDM) is a method used mainly with drugs having a narrow therapeutic range, where the patient's drug level is monitored regularly in order to ensure that the level of the drug in the bloodstream does not reach levels more likely to cause AEs [134]. Many drugs also have monitoring systems of laboratory results that ensure that a marker for a particular AE is being kept within normal limits. Such is the case with clozapine, where white blood cell counts need to be monitored in patients on a regular basis while using the medication[133].

5.1.2.3 Registries (R) are used where prescribers and/ or patients of a drug are required to be enrolled in a registry so that restrictions and conditions can be monitored or, screening for abnormal laboratory test results maintained. Such is the case with isotretinoin [135]

5.1.2.4 The Black Triangle Scheme (BTS) is a process whereby newly marketed drugs in the UK are assigned an inverted black triangle to indicate that they are new drugs and that reporting of AEs to the regulatory authority is encouraged. This black triangle is present within various formularies where the drug is listed, compendiums, as well as on advertising material [136].

5.1.2.5 Education Programs(EP): In some cases, there are interventions implemented by a Health Institution whereby patients and / or prescribers are provided education on a product, and its side effects, at the point of prescription or dispensing. This ideally results in swift action, and fewer AEs.

5.1.2.6 Informed Consent(IC): This process can also occur at the point where the patient is prescribed and / dispensed a drug product. E.g. the sponsor could choose to develop a patient agreement where

before receiving the product, the patient formally acknowledges their understanding of a contraindication [137]

5.1.2.7 Patient Alert Cards(PtAC)*:* Although patient reports have been accepted by regulatory agencies in regions such as Canada (Health Canada) and the USA (FDA) for several years, it was not until October 2005 that non-Healthcare professionals nationwide in the UK were able to report AEs directly to their regulatory authority, MHRA (Medicines and Healthcare Products Regulatory Agency) through the Yellow Card System (established in 1964). Other interventions (patient alert cards) have been created based on this Yellow Card System [138].

5.1.2.8 Education Material(EM): Also at the point of dispensing a product, written information can be provided to the patient in order to better educate the patient on the potential AEs associated with the drug. An example of this would be Medication Guides implemented by the FDA in 1999. They are distributed to outpatients at the time of product dispensing to provide additional education on risks of product use. [137]

Dear Health Care Professional Letters (DHCP Letter) are drafted by the manufacturer and regulator of a product, and disseminated to Health Care Professionals to convey important drug safety information. agency[139,140]

Public advisory warnings, and safety alerts also occur with marketed drugs and often follow the dissemination of a DHCP Letter. These warnings / alerts are generally placed on a regulatory agency's website or disseminated to interested members of the public with drug safety newsletter subscriptions. The general media may also obtain the information and relay it to the general public[9, 10].

Medication guides, Dear Health Care Professional Letters, Regulatory agency safety warnings / alerts, Public advisory warnings, and Medication guides are all categorised as Education material.

5.1.2.9 Black Box Warnings(BBW) are issued exclusively by the FDA in the USA, with extremely serious adverse reactions, or if Education materials are found to be ineffective. A Black Box Warning is the sternest warning by the U.S. FDA that a medication can carry and still remain on the market It is named for the black border surrounding the text of the warning that will appear on the package insert, label and other literature describing the medication (e.g., magazine advertising). In addition, a medication guide will be mandated by the FDA for the product of interest [141].

5.1.2.10 Product Withdrawals(W): Failing all efforts to minimise the risk of an adverse reaction, a regulatory agency may require a company to withdraw a product from the market as a last resort. In this article, only product withdrawals that were regulatory agency-mandated were considered as risk minimisation interventions. In extremely rare situations, a product may be re-introduced to the market post-withdrawal, with a specific and stringent risk management plan in place. These are usually in the form of a Restricted Distribution or a Registry.

5.1.3 Guidelines on Therapeutic Risk Management

Although Regulatory Authorities have issued guidance documents for drug manufacturers concerning pharmacovigilance quite some time ago (1991 in Canada), guidelines concerning Therapeutic Risk Management have only recently been integrated into the regulatory process by both the USA, and within Europe in 2005[9,10]. Here the FDA for example outlines RMIs as processes or systems intended to minimize known risks with the goal of :

Communicating particular information regarding optimal product use

Providing guidance on prescribing, dispensing, and/or using a product in the most appropriate situations or patient populations.

Not all drug products are the subject of RMIs, as only those posing particular safety concern who have received an evaluation and affirmation of the need, shall have them applied.

Also mandated in the guidances, are directives concerning the evaluation of the RMIs. These are provided in order to ensure that the resources invested in them are actually achieving the desired goals of continued benefits with minimized risks. Consequently each RMI should also have a plan for periodically evaluating its effectiveness after implementation [10] .

Canada is aware of the benefits and importance of incorporating Risk Management Planning throughout the entire life cycle of a drug product, and in February of 2009 posted a notice concerning implementation of Risk Management Planning and their intent to follow International guidances on Pharmacovigilance processes [142]. These regulatory changes involve the implementation of well-defined risk evaluation stakeholders in the management of potential and identified risks associated with medicines.

Due to the novelty of this subject, many drug manufacturers, as well as regulators, are still uncertain of what Risk Minimisation Interventions are available for use; which are appropriate for the various products; and consequently what interventions should be incorporated in a particular product's Risk Management Plan. Furthermore, the use of databases for these analyses is a promising approach to observing whether RMIs were in fact efficient at reducing the risk associated with the drug products.

5.2 Review of risk minimization interventions

5.2.1. Objectives and hypothesis

The systematic review, was a review of the literature and regulatory websites that would characterise RMIs used by industry, regulators, and institutions. In this review, we set out to:

(1) Identify the RMIs published in the literature, in the past and present on a global basis.

(2) Identify the knowledge gaps in the methodology and databases used for implementation and evaluation of RMIs.

(3) Determine whether the issuance of regulatory guidelines concerning risk management had an influence on the type and/ or frequency of risk minimisation interventions being used.

Our main hypothesis of this review was that the introduction of guidelines on Therapeutic Risk Management would have increased the number and quality of RMIs being implemented in the field.

5.2.2 Methods

We collected the following information from Embase and MEDLINE literature sources, and regulatory websites concerning RMIs that were implemented and/ or published between January 2000 and December 2009:

Nature of the RMI, target population, therapeutic area as per the Anatomical Therapeutic Chemical (ATC) classification system, AE(s) of special interest, regulatory region, and year of publication/posting. The characteristics of the RMIs were also compared across two five-year time periods: before the publication of the guidances (pre-guidances period: 2000-2004) and after the implementation (post-guidances period: 2005-2009).

5.2.3 Results

A total of 119 unique interventions were identified in the literature (54 published in 2000 -2004, and 65 published in 2005 - 2009). Interventions included Education Material (n=37, 31%), Black Box Warnings (n=22, 19%) and Therapeutic Drug Monitoring (n=11, 9%). The Website review produced a total of 1,112 interventions: 326 posted between 2000 and 2004, and 786 between 2005 and 2009. The main interventions observed were: Education Material (n=956, 86%), Black Box Warnings (n=45, 4%) and Withdrawals (n=39, 4%). For the literature review the pre and post guidances values of the three main RMI categories were as follows: Education material n=13 (24%) vs. n=24 (37%); Black box warning, n=6 (11%) vs. n=16 (25%); TDM n=6 (11%) vs. n=5(8%). For the website review, these numbers were the following: Education material n=279 (86%) vs. n=677 (86%); Black box warning, n=20(6%) vs. n=25 (3%); TDM n=5 (1.5%) vs. n=14 (1.8%). In the literature review, the distribution of RMI ATC between the two five-year time periods remained relatively consistent. A similar trend was seen with the RMI AE SOC category.

5.2.4 Discussion

Strengths and Weaknesses

This comprehensive review is the first of its kind, and to our knowledge, there are no publications which specifically summarise RMIs over this length of time, or that attempt to analyse the effect of the publication of guidances. Secondly, this article is a systematic and aggregate analysis of various features of RMIs, and no other article has taken on such a comprehensive approach at detailing and analysing trends concerning the RMIs published within the literature. Finally, the global perspective

taken with this review permits its application world-wide as the information is relevant across regions and can be used by many countries for RMI information.

Although the website review was quite detailed, the search is not completely exhaustive for a few reasons: (1) There were challenges concerning access to data. For example PMDA's website, only provides information from 2004 onwards. This could potentially bias the results with regards to the post-guidances numbers of the website review (2) Only a selected number of the regulatory authorties' websites were reviewed. Which could exclude RMIs specific to the individual EU countries websites not posted in the English language were also excluded which could result in the exclusion of important RMIs, however the fact that the EMA site was also searched expectantly included information for many of the non-English speaking EU countries; Particular RMI classification, and categorizing could also lead to discrepancies concerning the results of this review versus other reviews that may be conducted in the future.

The fact that the USA and EU are the two regions that implemented the guidances in itself would imply that they most likely would increase their RMIs post-guidances. In fact, both regions created dedicated websites for Risk Minimisation Activities (Medication Guides and approved REMS in the USA; and approve Risk Management Plans in the EU). This was indeed the case with the USA for both the literature and website reviews, however the EU only reflected an increase in their website review RMIs. The USA also has a unique RMI step in the black box warning which other countries do not have. This could be adding an extra RMI to the life cycle of a drug which would not exist in other countries. The large proportional increase of RMIs observed in the USA region in the literature review

but not the website review could be largely due to the fact that there are many more journals available in the USA as opposed to the rest of the world and consequently a publication bias. Thus, a literature review provides a larger source of US information as opposed to Canadian or European information.

A specific look at RMIs implemented in Canada shows that there is a large deficiency with regards to literature sources. This could in part be explained by publication bias, however there also seems to be a lack of research concerning this aspect of risk management by Canadian researchers. This suggests great potential for future research in this area. During the pre-guidances period of the website review, Canada displays a large role in the proportion of global RMIs, and is in fact the region with the majority of RMIs during that time period, the USA following closely behind. This changes drastically during the post-guidances period: although the number of RMIs that Canada produces is approximately the same, the increase in RMIs by other regions, offsets Canada's proportion. Again, the fact that the EU and USA increased their alertness concerning RMIs and risk management plans is believed to be the major reason for this [9,10]. Although Health Canada has recognized the importance of risk management planning, it is still apparent that they have not been able to implement these activities as favourably as would be ideal.

Risk minimisation gaps identified

To mirror the requirements of the FDA's Pediatric Research Equity Act (PREA) [143], which sets out requirements concerning pediatric assessments for drug applications/approvals: post-marketing activities for products with particular safety risk being used in children, should also have RMIs targeting children, which should be active throughout the life cycle of the drug. Within the risk management guidances both the FDA and the EMA encourage the development of additional risk minimisation activities designed to address safety concerns in instances where particular populations

may be at risk. The FDA and EMA outline that such target populations include among others: children, the elderly, and pregnant or lactating women. It is believed that for this reason we see some RMIs targeting children and pregnant women. However, this number is still very low considering the guidances. Furthermore, the extremely low number of RMIs targeting the elderly is particularly concerning, thus highlighting an important gap in the current conduct of RMIs.

Effect of regulatory guidances on RMI distribution

This systematic review implies that the guidances on therapeutic risk management did lead to an important increase in the number of RMIs implemented within the USA and published in the literature. There was also an important increase among website review RMIS of the regions of the USA, EU and Japan. The regulations did not appear have an effect on the distribution of RMI types across the pre- and post-guidances periods for either the literature review or the website review. Furthermore, the literature review did not show variation in the distribution of the ATC Classifications, or the AE SOC classes of the target drugs for the RMIs in the pre-vs. post-guidances period. Although this is a work in progress, it appears that for the first five years post issuance, the guidances have only had an effect on increasing overall numbers of RMIs for only some of the regions.

Future Perspectives

The immediate next step of this analysis is actually a parallel ongoing study to identify the methods used to assess the effectiveness of these RMIs as is required by the guidances on Risk Management. Determining which are the most effective of the RMI's based on the results of observed studies, and which are the most convenient methods to be used with the various types of RMIs. Future potential

studies could involve a detailed account of the methodological challenges faced by those who wish to assess the RMI effectiveness. What aspects to account for during the analyses, identifying gaps in the methods, and proposing means of overcoming them. Finally, this is an analysis with potential for longevity as the pharmaceutical, healthcare, and regulatory industries overall could also benefit from the continued reviews of RMIs going forward.

5.2.5 Conclusions

In conclusion, the website review found that the guidances on therapeutic risk management did lead to an important increase in the number of RMIs implemented within the USA, EU and Japan. However the literature review only showed an increase within the USA. The discrepancy with the literature review vs. the website review demonstrates the existence of publication bias. Although interventions found in the literature are fewer in number, more innovative interventions and variety can be obtained from these sources. Interventions specific to drugs, therapeutic areas or populations are rare. More RMIs specific to drugs, therapeutic areas and most importantly: specific populations, need to be conducted in order to better comply with the risk management guidances.

5.3 RMI Review Article: Impact of regulatory guidances and drug regulation on risk minimisation interventions in drug safety: a systematic review

Contributions of co-authors to article:

As Principal researcher of this review, Lenhangmbong Nkeng (LN) had major contributions to the study: She proposed the idea of a review of risk management processes; designed and coordinated the review strategy; performed the MEDLINE review portion of the literature review, and the entire website review; completed initial extraction of data, interpreted the results; and drafted the manuscript.

Anne-Marie Cloutier assisted with the strategy for literature and website searches completed review of the EMBASE database for the literature review, peer-reviewed a portion of the sources which were excluded by LN, proof-read the drafted article and provided feedback on the manuscript.

Camille Craig peer-reviewed the remainder of the sources which were excluded by LN, proof-read the drafted article and provided feedback on the manuscript

Dr. Jacques Lelorier reviewed the article and provided feedback on results, interpretation, and discussion of the manuscript.

Dr. Yola Moride proposed the focus of the review to the subject of “risk minimisation interventions”, provided guidance on the research strategy, reviewed the article, and provided comments and additional ideas for inclusion in the manuscript.

Impact of regulatory guidances and drug regulation on risk minimisation interventions in drug safety: a systematic review

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There are no conflicts of interest to declare for any of the authors.

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Country Codes as per ISO 3166:

USA=United States of America; GBR=United Kingdom; DEU=Germany; SWE=Sweden; FRA=France; CHE=Switzerland; DNK=Denmark; NLD=Netherlands; ESP=Spain; AUS=Australia; CAN=Canada; SGP=Singapore; JPN = Japan

* EU = European Union member states

INTL = International

UNK = Unknown

Regulatory Agency Accronyms

TGA = Therapeutic Goods Administration; PMDA = Pharmaceutical and Medical Devices Agency; MHRA = Medicines and Healthcare Products Regulatory Agency; EMA = European Medicines Agency; FDA = Food and Drugs Administration; HC = Health Canada

RMI Accronyms

EM =Education material; BBW=Black box warning; TDM=Therapeutic Drug Monitoring; EP=Education program; RD=Restricted distribution**;** IC=Informed consent; W=Withdrawal, R=Registry; PtAC=Patient Alert Card; PtR - Patient registry PG=Pharmacogenetics**;** BTS=Black Triangle Scheme.

Drug ATC:

NS = Nervous System; A = Alimentary tract and metabolism; B = Blood and blood forming organs; L = Antineoplastic and immunomodulating agents;

D = Dermatologicals; C=Cardiovascular system

Comb = Combination

AE SOC:

CV=Cardiovascular disorder; N=Neoplasms, benign, malignant and unspecified; Psy=Psychiatric disorders; Con= Congenital, familial, and genetic disorders; Hep=Hepatobiliary disorders; Blood = Blood and lymphatic system disorders

Div= Diverse (combination of AE SOC)

Impact of regulatory guidances and drug regulation on risk minimisation interventions in drug safety: a systematic review

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ABSTRACT

Background: Therapeutic risk management has received growing interest in recent years particularly since the publication of regulatory guidances in 2005 and 2006, paralleled with a change in drug regulation. The characteristics of risk minimisation interventions (RMIs) that have been implemented or approved remain inadequately explored.

Objective: To review RMIs published in the literature or posted on regulatory agency websites over the past 10 years, and to assess whether the publication of regulatory guidances on risk management is associated with changes in the number and types of interventions.

Methods:

Sources were searched for RMIs published/posted between January 1, 2000 and December 31, 2009. For the literature search, MEDLINE and EMBASE databases were used using key words related to Drug Safety (i.e. "Drug Toxicity") AND the individual risk minimisation intervention names. The website review involved searches of major regulatory authority websites such as: European Medicines Agency, USA Food and Drug Administration, Canada's Health Canada, the United Kingdom's Medicines and Healthcare Products Regulatory Agency, Japan's Pharmaceutical and Medical Devices Agency, and Australia's Therapeutic Goods Administration. The following eligibility criteria were applied for inclusion in the review: Published/posted between 2000 and 2009 inclusive; involving drug

products; use in humans; involving risk minimisation interventions, or tools used to increase the reporting of adverse events. Natural healthcare products, devices, diagnostic chemicals, pregnancy registries without follow-up, medication errors, and products not used as therapy for illness, were not retained. For each source, the following characteristics were extracted: nature of the intervention, target population, therapeutic area, adverse event(s) of special interest, country/ regulatory agency, and year of publication.

Results: A total of 119 unique interventions were identified in the literature (54 published in 2000 - 2004, and 65 published in 2005 - 2009). Interventions included Education Material (n=37, 31%), Black Box Warnings (n=22, 19%) and Therapeutic Drug Monitoring (n=11, 9%). The Website review produced a total of 1,112 interventions: 326 posted between 2000 and 2004, and 786 between 2005 and 2009. The main interventions observed were: Education Material (n=956, 86%), Black Box Warnings (n=45, 4%) and Withdrawals (n=39, 4%).

Limitations:

Additional regulatory resource websites were available in the post-guidances periods that were not available in the earlier years of the pre-guidances periods, and may bias the post-guidances results. Also not all global regulatory websites were searched. Finally only English language websites were searched, limiting the variation of RMIs observed. Classification and categorizing for this particular review may not be consistent with future reviews by other researchers.

Conclusion: The USA is the sole region with a substantial increase in *published* risk minimisation interventions during the post-guidances period while EU, Japan, and USA all indicated an increase in the number of interventions on their *websites*.

Background

Risk minimisation interventions (RMIs) are tools that aim at enhancing the benefit-risk of medicines beyond product labelling[1]. In the broad spectrum of RMIs, one may find educational interventions, on one end, and more stringent programs, such as Restricted distribution, on the other end. Among the most well-known education interventions are Dear Health Care Professional (DHCP) Letters issued by drug manufacturers or regulatory agencies,[3] Black Box Warnings, Medication guides, Regulatory agency safety warnings / alerts, and Public advisory warnings. Therapeutic Drug Monitoring (TDM) is another type of RMI used mainly for drugs that have a narrow therapeutic range. The patient's blood level of the drug is monitored in order to ensure that it does not reach levels more likely to cause adverse events (AEs)[4]. Registries are also used where prescribers and/ or patients are enrolled so that restrictions can be monitored or, screening for abnormal test results maintained. RMIs may target prescribers (e.g. education and training) or patients (patient alert cards, informed consent), and can be implemented by different stakeholders such as drug manufacturers, regulatory authorities, or a healthcare institution.

Although RMIs have been in use for several decades, it was not until 2005-2006 that both the FDA and the EMA introduced their guidances on therapeutic risk management. The guidances define a risk management plan (RMP), conditions of requirement, and, risk minimisation activities that may be required in instances of specific safety concerns[1,2].

Since then, the field of therapeutic risk management has received growing interest. Due to the novelty of the subject, however, the characteristics of the various RMIs that have been implemented remain poorly explored. Although reviews have been published in the literature [5,6,7] few have aimed at

comprehensively examining trends of RMIs, or the effect of the publication of risk management guidances on their frequency and type. Leiderman [5]performed a review of selected examples of risk management programs and RMIs implemented prior to the introduction of guidelines. However the review was not comprehensive or systematic, nor was there the attempt or the ability to examine the effect of the regulatory guidances on the characteristics of RMIs. Similarly, the review by Hirst et al [7]summarized some of the RMIs used between 1997 and 2005, with a main focus on product withdrawals during that time period (n=22). In the Wise et al. review[6], the authors' focus was the overall field of pharmacovigilance, and tools used for such. Consequently, the review was general and not specifically geared towards risk minimisation.

Objectives

Our study aimed at characterizing RMIs implemented during the five years before, and the five years after, the introduction of the regulatory guidances on risk management. This was achieved through the conduct of a systematic review with the following specific objectives: (1) To identify the RMIs published in the literature or posted on selected regulatory agencies websites; (2) To describe the RMIs with respect to the target population, drug class, safety issue(s), nature of the intervention; (3) To determine whether the issuance of regulatory guidelines on risk management had an influence on the type and/ or frequency of RMIs being implemented.

Methods

Search strategy

The review was conducted through the literature as well as agency websites, and followed the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies [8]. The literature search was conducted using MEDLINE and Embase databases. Medical Subject Heading (MeSH) terms were used where possible. However, few were located through individual RMI names. In addition, terminology varied slightly for the MEDLINE and Embase databases. Consequently, key words related to the following subjects were used: "Drug toxicity" (MeSH term) AND "Patient education" (MeSH term), OR"HCP education", OR"Prescriber education", OR"Patient alert card", OR"Patient registry", OR"Medication guide", OR"Drug legislation" (MeSH term), OR"Informed consent" (MeSH term), OR"Restricted distribution", OR"Physician authorisation", OR"Drug monitoring" (MeSH term), OR"Dear Health Care Professional Letter", OR"Dear Doctor Letter", OR"Black Box Warning". All articles, including review articles, were scanned for potential relevant references (snowballing). The Embase and MEDLINE initial reviews were performed by two separate researchers. The MEDLINE review was completed on January 22, 2010 by LN and the Embase review on January 29, 2010 by AMC. The resulting articles were scanned, and snowballing was performed by one individual (LN). The excluded articles were then scanned by one of two secondary individuals (AMC and CC) to ensure that that any qualifiable RMIs remained. Any disagreements were resolved with a majority (two out of three) decision (LN, AMC, and CC).

The website review involved an initial search by one researcher (LN) of the following agency sites with the initial data collection process for each website completed on the dates indicated: Health

Canada - safety alerts / advisory warnings (http://www.hc-sc.gc.ca/; June 16, 2010); EMA (Europe approved RMPs http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124; August 6, 2010); FDA (USA approved Risk Evaluation and Mitigation Strategies (REMS), and Medication Guides); FDA safety alerts / advisory warnings(http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/; July 9, 2010); Therapeutic Goods Administration (TGA) (Australia) advisories (October 13, 2010); Medicines and Healthcare Products Regulatory Agency (MHRA) (UK) safety alerts / advisory warnings (http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/index.htm; September 20, 2010); Pharmaceutical and Medical Devices Agency (PMDA) (Japan) Pharmaceuticals Safety Information (http://www.pmda.go.jp/english/service/precautions.html; September 30, 2010). The excluded warnings / alerts were then scanned by one of two secondary individuals (AMC and CC) to ensure that the first had not excluded any important RMIs. Any disagreements were decided with a majority (two out of three) decision.

Eligibility criteria

To be included in the review, RMIs needed to have been published or posted between 1st January 2000 and 31st December 2009, involved drug products, use in humans, RMIs, or tools used to increase the

reporting of AEs. The RMI could be sponsored by any organisation (e.g. regulatory authority, commercial organization, or institution etc.) Natural healthcare products, devices, diagnostic chemicals, pregnancy registries without follow-up, medication errors, and products not used as therapy for illness, were not retained.

For each RMI, the following characteristics were extracted and recorded into a harmonised information matrix: nature of the RMI, target population, therapeutic area as per the Anatomical Therapeutic Chemical (ATC) classification system, AE(s) of special interest, regulatory region, and year of publication/posting. The characteristics of the RMIs were also compared across two five-year time periods: before the publication of the guidances (pre-guidances period: 2000-2004) and after the implementation (post-guidances period: 2005-2009).

Some RMIs involve a combination of different intervention types. For the review, if more than one RMI for a particular safety concern was published in a given year, they were counted as one RMI. Furthermore, only the most stringent component (e.g. Patient alert card or Restricted distribution), was retained for the synthesis of information. Regions for categorizing RMIs were based on regulatory jurisdictions (e.g. EU, USA, Canada, Japan, Australia). The region recorded corresponded to the site of the RMIs execution. If a source described an RMI as present in more than one region, it was considered an “international RMI”.

Classification of RMI types

Classifying the RMI types was completed in the following manner: Education materials comprised Dear Healthcare Professional Letters, Regulatory agency safety warnings / alerts, Public advisory warnings, and Medication guides. Patient alert cards included both the UK Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card reporting process, and patient alert cards themselves. Restricted Distribution incorporated restricted/controlled prescription and distribution; and Therapeutic Drug Monitoring (TDM) included both laboratory results' monitoring systems (to ensure that a marker for a certain AE is being kept within normal limits), as well as therapeutic drug monitoring of the drug concentration itself. Withdrawals included voluntary withdrawals, regulatory agency-mandated withdrawals, as well as suspensions.

Comparison of RMIs in the period before and after the regulatory guidances

The proportion of RMIs published before and after the regulatory guidances were compared through chi-square tests or Fisher's exact tests in instances of low numbers.

Results

Literature search

Figure I displays the results of the literature search. A total of 2,103 articles were initially identified from the bibliographic databases. Of these, 135 met the inclusion criteria, and another 34 sources were obtained from snowballing yielding 169 sources. After applying the inclusion / exclusion criteria listed above, a total of 119 distinct interventions were retained for the review. Since some

interventions were associated with more than one publication, only one source was retained. Information extracted into the harmonized matrix is found in the Literature Review Data Extraction Table (Appendix I).

In the pre-guidances period, 54 (45%) RMIs were published, while in the post-guidances period, there were 65 (55%). This increase was, however, not statistically significant (p-value = 0.313).

Table I displays the geographical distribution of publications. The majority of interventions were implemented in the USA (n=65, 55%) and the EU (n=22, 18%). Other regions included Australia (n=3, 3%), Canada (n=2, 2%) and, Singapore (n=1, 1%). There were nine sources (8%) that involved an RMI that was simultaneously implemented in more than one region (i.e. International). There were 17 RMIs (14%) for which the region of implementation was unspecified and therefore unknown.

Across the various regions, there were 11 different publications (each discussing an RMI), that together described a total of five duplicated RMIs implemented in different regions, i.e. RMIs of the same type, and same safety issue, however implemented in varying regions).

According to Table II, the three most frequent RMIs published in the literature were: Education material (n=37, 31%), Black box warning (n=22, 19%), Therapeutic Drug Monitoring (TDM) (n=11, 9%). These rankings were relatively consistent across pre- and post-guidances periods: Education material n=13 (24%) vs. n=24 (37%); Black box warning, n=6(11%) vs. n=16 (25%); TDM n=6 (11%) vs. n=5(8%); Education programs n=2 (4%) vs. n=7 (11%) for the pre- and post-guidances periods respectively.

There were 12 RMIs that were in fact a combination of different RMI types: Five combinations involved Restricted distribution in combination with either Registries alone or along with Education materials or Education programs. Four were in the pre-guidances period; Three combinations involved Informed Consent (2 pre-, and 1 post- guidances) in combination with either Education material, or TDM; Two groupings of TDMs were observed, one with an Education material, and the other with an Education program. Both were implemented in the pre-guidances period; One Black box warning was combined with an Education material in the post-guidances period, and one Patient alert card with an Education material also during the post-guidances period.

The distribution of the RMIs by ATC class, and subdivided into pre-guidances (2000-2004) and post-guidances (2005-2009) is displayed in Figure II. Most RMIs involved drugs of the nervous system (n=40, 34%), followed by the alimentary tract and metabolism (n=17, 14%), and finally blood and blood forming organs (n=9, 8%). The distribution of RMI ATC between the two five-year time periods remained relatively consistent. The System Organ Classes (SOC) of AEs of interest (as per Medical Dictionary for Regulatory Activities, MedDRA) are reported in Figure III, where the majority was simultaneously geared towards a combination of AE SOCs (n=45, 38%). Again the distribution of RMI AE SOC remained fairly consistent across the two five-year time periods.

Overall, 70% of RMIs published over the 10-year period applied to the general population (refer to Table III). The remaining 25 were specific to a sub-population, with eleven being women-specific and geared largely towards avoiding pregnancy and/or congenital malformations and teratogenic effects (n=6). These were mainly with medications such as isotretinoin and thalidomide. Other RMIs were specific to the paediatric population (n=10) (mostly for Nervous system drugs, n=7), and for the elderly (n=3, all involving Nervous system drugs).

Website search

Figure IV displays the results of the website review search. Altogether, 1,112 interventions were identified through the website review. In Table IV it is seen that the overall number of RMIs more than doubled, from 326 in the pre-guidances period to 786 during the post-guidances period. As shown in Table V, the most frequent RMIs observed from the website review were as follows: Education materials (n=956, 86%), Black box warnings (n=45, 4%), Withdrawals (n=39; 4%). This distribution was also generally consistent across the different regions. The overall regional distribution was as follows: USA n=538 (48%); Canada: n=258 (23%); EU: n=183 (17%); Japan: n=115 (10%) and Australia: n=18 (2%). Changes in regional distribution across periods are shown in Table IV.

Combination RMIs (n=41) were exclusive to three regions: EU (n=19), USA (n=12) and Canada (n=10). Among the combination RMIs, 9 involved Patient alert cards combined with Education programs and/or Education material, one of which was combined with TDM; 11 Withdrawals were combined mainly with Education materials, one including a TDM; 5 RMIs involved Restricted distribution in combination with Education programs and/or Education materials; 5 involved groupings of Black box warnings with Education materials; 5 TDM programs were combined primarily with Education materials, one including an Informed consent; 2 Registries were combined with Restricted distribution and/or Education material and; 1 involved a combination of informed consent and Education material. There was 1 informed consent that included a patient agreement, and 2 Education progam-Education material combinations.

Literature Review versus Website Review

The review revealed major differences between the results of the Literature Search and the Website Review. In Table I it is seen that in the literature search, the USA was the sole region with a substantial increase in published RMIs during the post-guidances period, n=25 (46%) and n=40 (62%), respectively for pre- and post-guidances period. However, from Table IV the website review shows that many regions increased their RMIs during the post-guidances period, namely USA n=127 (39%) and n=411 (52%), EU n=37 (11%) and n=146 (19%), and Japan n=24 (7%) and n=91 (12%) respectively for the pre-and post-guidances periods. The two most common RMIs used in both reviews were similar: Education materials and Black box warnings. The percentage of Education materials observed in the website review (n=956, 86%) was greater than those of the literature review (n=37, 31%), offsetting the percentages of all other RMIs. Such differences in numbers and characteristics according to data source suggest the presence of a publication bias.

Discussion

From the literature review alone, there was no significant difference in the overall number of RMIs published in the literature during pre-and post-guidances periods. However, the USA had a large increase between these time periods in their numbers. This could in part be due to the fact that the USA is one of the two regions that implemented the guidances, and possibly both the FDA and US drug manufacturers became more active in this regard. In addition, the USA took additional measures to

launch a web page dedicated to the posting of approved REMS as well as medication guides. This could in part be a reason for their apparent increased number as other regions, such as Canada, continue to display only safety alerts, and do not have additional web pages for approved RMPs that may be implemented. Finally, the USA has a unique RMI step in the black box warning which other countries do not have. This could be adding an extra RMI to the life cycle of a drug which would not exist in other countries. The website review results differ: There is a clear increase in RMIs during the post-guidances period, and the increase of RMIs is reflected in two additional regions: EU and Japan. The large proportional increase of RMIs observed in the USA region in the literature review but not the website review could be largely due to the fact that there are many more journals available in the USA as opposed to the rest of the world. Thus, a literature review provides a larger source of US information as opposed to Canadian or European information. The literature review shows that population-specific RMIs mainly involve two sub-populations: Women and paediatrics. The RMI types targeting women do appear to be population-specific, displaying a predominance of Education programs. Within the guidances both the FDA and the EMA encourage the development of additional risk minimisation activities designed to address safety concerns in target populations versus those populations that have been included in clinical trials. Such target populations include among others: children, the elderly, and pregnant or lactating women. It is believed that for this reason we see some RMIs targeting children and pregnant women. However, this number is still very low considering the guidances. Furthermore, the extremely low number of RMIs targeting the elderly is particularly concerning, thus highlighting an important gap in the current conduct of RMIs.

This comprehensive review is the first of its kind, and to our knowledge, there are no publications which specifically summarise RMIs over this length of time, or that attempt to analyse the effect of the

publication of guidances. Secondly, this article is a systematic and aggregate analysis of various features of RMIs, and no other article has taken on such a comprehensive approach at detailing and analysing trends concerning the RMIs published within the literature. Finally, the global perspective taken with this review permits its application world-wide as the information is relevant across regions and can be used by many countries for RMI information.

Although the website review was quite detailed, the search is not completely exhaustive for a few reasons: (1) There were challenges concerning access to data. For example, the Japanese Regulatory Authority, PMDA, only provides information on its website as of 2004 onwards. This could potentially bias the results with regards to the post-guidances numbers of the website review as the site could be missing some RMIs that the PMDA may have implemented before 2004; (2) Only a selected number of the regulatory authorties' websites were reviewed. For example, some RMIs specific to the individual EU country regulators could be missing from this review. This review also excludes websites that were not posted in the English language. All of these facts could result in the exclusion of important RMIs, however the fact that the EMA site was also searched expectantly included information for many of the non-English speaking EU countries; (3) It is important to note that since the initial search of the Health Canada Website (June 16, 2010), safety alerts originating prior to 2004 are no longer available on the site itself and need to be requested from Health Canada directly. For the review, if more than one RMI in a particular region, for a particular safety concern, was published in a given year, they were counted as one RMI. Furthermore, only the most stringent type (e.g. Patient alert card or Restricted distribution), was retained for the synthesis of information. This assumption could

also lead to discrepancies concerning the results of this review versus other reviews that may be conducted in the future.

Conclusion

This systematic review implies that the guidances on therapeutic risk management did lead to an important increase in the number of RMIs implemented within the USA, EU and Japan. However the discrepancy with the literature review demonstrates the existence of publication bias. From the literature review, it is clear that many RMIs are simultaneously geared towards heterogeneous AEs, drug classes, and patient sub-populations. More RMIs would need to be published in order to better assess trends in RMI characteristics. Although interventions found in the literature are fewer in number, more innovative interventions and variety can be obtained from these sources than on the website review.

REFERENCES

[1] U.S. Food and Drug Administration. Guidance for Industry Development and Use of Risk Minimization Action Plans [online]. Available from URL: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf. [Accessed 2010 October 1]

[2]European Medicines Agency Guideline on Risk Management Systems for Medical Products for Human Use. [online]. Available from URL: http://www.ema.europa.eu/pdfs/human/phv/11590605en.pdf. [Accessed 2010 March 11]

[3] Health Canada Guidance for Industry. Issuance of Health Professional Communication [online]. Available from: http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2010-guid-dir_indust_hppc-cpsp/index-eng.php. [Accessed 2011 Sep 28]

[4]Touw DJ, Neef C, Thomson, AH, et al. Cost Effectiveness of Therapeutic Drug Monitoring: an update. EJHP Science. 2007 4(13); 83-91

[5]Leiderman DB. Risk management of drug products and the U.S. Food and Drug Administration: Evolution and context. Drug and Alcohol Dependence 2009 ; 105S S9–S13

[6] Wise L, Parkinson J, Raine J et al. New approaches to drug safety: a pharmacovigilance tool kit. Nat Rev Drug Discov 2009; 8(10):779-82

[7]Hirst C, Cook S, Wanju D. A call for international harmonization in therapeutic risk management. Pharmacoepidemiol Drug Saf 2006; 15: 839-49

[8] Liberati A, Altman G, Tetzlaff J et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Medicine 2009. 6(7); 1-29

LITERATURE REVIEW SOURCE REFERENCES

1. Food and Drug Administration. FDA talk paper: Janssen Pharmaceutica stops marketing cisapride in the US [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3634b1a_tab4a.htm [Accessed 2010 May 4]

2. Lotronex.com. Prescribing program for Lotronex. Pharmacist information [online]. Available from URL: http://www.lotronex.com/Physicians/Prescribing/ [Accessed 2010 May 4]

3. Celgene. S.T.E.P.S. prevention and protection [online]. Available from URL: http://www.thalomid.com/steps_program.aspx [Accesed 2010 May 4]

4. Failings in treatment advice, SPCs and black triangles [editorial]. Drug Ther Bull, 2001. 39(4): 25-7.

5. 'Black-box' warning and letter are insufficient to protect patients, study finds [editorial]. Am J Health Syst Pharm, 2001. 58(3): 197-200.

6. The Food and Drug Administration. Tumor necrosis factor-alpha blockers (TNF blockers), Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab). [online] Available from URL http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm163195.htm [Accessed 2010 May 6]

7. Agence Francaise de Securite Sanitaire des Produits de Sante, les lettres aux prescripteurs, Eprex®: information importante de pharmacovigilance. 2002 December 17 [online]. Available from URL: http://www.afssaps.fr/Infos-de-securite/Lettres-aux-professionnels-de-sante/EPREX-R-information-importante-de-pharmacovigilance [Accessed 2010 May 4]

8. Wichtige Information zur Arzneimittelsicherheit ERYPO®/EPREX® (Epoetin alfa) Art der Anwendung—nur intravenöse Applikation bei Patienten mit Nierenversagen & Erinnerungshinweis betreffend Lagerung—bei 2-8°C aufbewahren. 2001 December 11. Available from URL: http://www.akdae.de/20/40/Archiv/2002/95_20021211.pdf. [Accessed 2010 May 5]

9. Eprex® (Epoetin Alfa) and pure red cell aplasia - contraindication of subcutaneous administration to patients with chronic renal disease [online]. Available from URL:

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2015723. [Accessed 2010 May 4].

10. PRCA update 2002 [online]. Available from URL: http://www.amgen.com/patients/prca.html. [Accessed 2010 October 29]

11. Important safety information—EPREXTM (epoetin alfa)—Janssen-Ortho Inc. Health Canada. 26 November 2001 [online]. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2002/eprex_pa-ap-eng.php. [Accessed 2010 May 4]

12. Important Drug Safety Update Eprex (epoetinalfa)—pure red cell aplasia (PRCA, Erythroblastopenia). Health Canada. 2002 June 25 [online]. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfbdgpsa/pdf/medeff/eprex_2_hpc-cps_e.pdf. [Accessed 2010 May 10]

13. Danco Laboratories. Open letter to health care providers. 2002 April 19 [online]. Available from URL: www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf [Accessed 2010 May 10]

14. FDA strengthens warnings for droperidol. 2002 [online]. Available from URL: http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01123.html. [Accessed 2010 May 9]

15. Suicide risk warning for children now extended by CSM to cover venlafaxine [editorial]. Pharmaceutical Journal 2003; 271(7268): 395.

16. Patients to have new role in improving methotrexate safety, says NPSA [editorial]. Pharmaceutical Journal 2003; 270(7256): 3.

17. Merck. Paget's patient support program [online] Available from URL: www.fosamax.com/fosamax/hcp/patient/paget.html [Accessed 2010 May 8].

18. Paroxetine review makes safety warnings [editorial]. Pharmaceutical Journal 2004; 272(7297): 534.

19. US Food and Drug Administration: 2004 Safety Alert: Zyprexa (olanzapine) [online]. Available from URL: www.fda.gov/medwatch/SAFETY/2004/zyprexa.htm. [Accessed 2010 May 2]

20. Calcineurin inhibitors: Black box warning for pimecrolimus and tacrolimus [editorial]. [German]. Deutsche Apotheker Zeitung 2005; 145(12): 50-52.

21. FDA advisory committees recommend marketing of COX-2 inhibitors with 'black box' warning [editorial]. Formulary 2005; 40(3): 76-77.

22. Impotence drugs receive blindness warning [editorial]. Nat Rev Drug Discov 2005; 4(8): 618-619.

23. Stronger warnings needed for asthma treatments [editorial]. Nat Rev Drug Discov 2005; 4(8): 618.

24. European COX-2 review recommends new warnings [editorial]. Pharmaceutical Journal 2005; 275(7356): 5.

25. FDA issues public health advisory recommending limited use of Cox-2 inhibitors. S Afr Med J 2005.;95(2): 92.

26. Food and Drug Administration, "2005 Safety Alert: Natrecor (nesiritide)" 2005 July 13 [online] Available from URL: http://www.fda.gov/medwatch/SAFETY/2005/natrecor2_DHCP.htm [Accessed 2010 May 12]

27. FDA Public Health Advisory: Strengthened risk management program for isotretinoin [online]. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm . [Accessed 2010 May 10]

28. Dear Health Care Provider letter. Important drug warning and new information for Clozaril(clozapine). Novartis Pharmaceuticals Corporation, 2005 December [online]. Available from URL: http://www.fda.gov/medwatch/safety/2006/Clozaril_chart_letter_final12-2005.pdf [Accessed 2010 May 5]

29. US Food and Drug Administration: FDA Public Health Advisory: Deaths with antipsychotics in elderly patients with behavioral disturbances, 2005April 11 [online]. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm [Accessed 2010 May 6]

30. Alert for Healthcare Professionals Valdecoxib (marketed as Bextra) [online]. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm [Accessed 2010 May 9]

31. The Food and Drug Administration. Public Health Advisory: suicidal thinking in children and adolescents being treated with Strattera (atomoxetine). 2005 September 29. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm. [Accessed 2010 May 10]

32. Pharmacists advised of atomoxetine risk [editorial]. Pharmaceutical Journal 2005; 274(7336): 166.

33. The Food and Drug Administration, FDA Public Health Advisory: Suicidality in Adults Being Treated with Antidepressant Medications," 2005 June 30 [online]. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm. [Accessed 2010 May 6]

34. Medication Guide: Coumadin tablets (warfarin sodium tablets, USP) crystalline. 2006 [online]. http://www.fda.gov/medwatch/safety/2006/coumadin_medguide.pdf. [Accessed 2010 May 7]

35. The Food and Drug Administration.FDA proposes new warnings about suicidal thinking, behavior in young adults who take antidepressant medications 2 May 2007 [online] Available from URL: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01624.html. [Accessed 2010 May 7]

36. Health Services Authority, Singapore Government product safety alert. Update on Eprex and pure red cell aplasia [online]. Available from URL: http://www.hsa.gov.sg/docs/safetyalert_epoetinalfa_Dec02.pdf [Accessed 2010 May 11]

37. Epoetin alfa and pure red cell aplasia. Australian adverse drug reactions bulletin. Volume 21, Number 3. August 2002[online]. Available at http://www.tga.gov.au/hp/aadrb-0208.htm#a4. [Accessed 2010 May 11]

38. Safety concerns for two big anemia drugs [editorial]. Nursing, 2008. 38(10): 12.

39. Tegaserod: withdrawal from the world market. A treatment for constipation with cardiovascular adverse effects [editorial]. Prescrire Int 2008; 17(95): 112-3.

40. U. S. Food and Drug Administration. Information on exenatide (marketed as Byetta®) 2008 [online]. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm [Accessed 2010 May 5]

41. Suicidality and antiepileptic drugs: FDA alert [online]. Available from URL: http://www.fda.gov/cder/drug/infopage/antiepileptics/default.htm.). [Accessed 2010 May 9]

42. MHRA Drug Safety Update on Exenatide 2008[online]. Available from URL: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON015025. [Accessed 2010 May 7]

43. U. S. Food and Drug Administration. Information for Healthcare Professionals suicidality and antiepileptic drugs. 2008 January 31. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm [Accessed 2010 May 7] .

44. PRCA update [online]. Available from URL: http://www.amgen.com/patients/prca.html. [Accessed 2010 May 7]

45. U.S. Food and Drug Administration. Complete response and safety labeling change order. 2008 July 30 [online]. Available from URL: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110271.pdf [Accessed 2010 Feb 9]

46. Hitt E. Botulinum Toxin Safety Warnings Updated and Name Changes Issued. 2009 [online]. Available from URL: http://www.medscape.com/viewarticle/706934 [Accessed 2010 Feb 10]

47. U.S. Food and Drug Administration Safety Alert. Simvastatin Used With Amiodarone 2008 [online. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm095009.htm. [Accessed 2010 October 28]

48. Aaronson D. The ‘‘black box’’ warning and allergy drugs. J Allergy Clin Immunol 2006; 117(1): 40-4

49. LaPointe ANM, Hammill BCA, DeLong E, Kramer JM, Califf RM. Evaluation of the dofetilide risk-management program. Am Heart J 2003;146(5): 894-901

50. Autret-Leca E, Jonville-Bera AP, and Cissoko H. Methods for studying drug risk during pregnancy. Archives de Pediatrie 2000; 7 Suppl 2: 404s-406s

51. Baumann P, Hiemke C, Ulrich S et al. Therapeutic Monitoring of Psychotropic Drugs: An Outline of the AGNP-TDM Expert Group Consensus Guideline. Ther Drug Monit 2004; 26(2): 167-170

52. Baumann P, Hiemke C, Ulrich S et al. The AGNP-TDM Expert Group Consensus Guidelines: focus on therapeutic monitoring of antidepressants. Dialogues Clin Neurosci 2005; 7(3): 231-47

53. Beltrani VS. The "black boxing" of protopic and elidel. Pediatr Asthma Allergy Immunol 2005; 18(2): 112-114

54. Bensouda-Grimaldi L, Jonville-Béra AP, Mouret E. et al. Isotretinoin: compliance with recommendations in childbearing women. Ann Dermatol Venereol 2005; 132(5): 415-23

55. Bourke JL, Bjeldbak-Olesen I, Nielsen PM et al. Joint charts in drug handling. Toward increased drug safety. Ugeskr Laeger 2001; 163(39): 5356-60

56. Brinker A, Kornegay C, and Nourjah P. Trends in adherence to a revised risk management program designed to decrease or eliminate isotretinoin-exposed pregnancies: Evaluation of Accutane SMART Program. Arch Dermatol 2005; 141: 563-569

57. Brown P. and Faloon L. The incidence and reporting of adverse drug reactions in the Division of Psychiatry. Pharm World Sci 2001; 23(5): 181-2.

58. Buck ML, Gurka MJ, and Goodkin HP. Postmarketing modifications in the safety labeling of the new antiepileptics. Neurology 2007; 68(18): 1536-7

59. Calhoun BC and Harrison DJ. Challenges to the FDA approval of mifepristone. Ann Pharmacother 2004; 38(1): 163-8

60. Castaneda CP, Zeldis JB, Freeman J et al. RevAssist: A comprehensive risk minimization programme for preventing fetal exposure to lenalidomide. Drug Saf 2008; 31(9): 743-752

61. Charatan F. FDA advisory panels recommend Lotronex be put back on market. BMJ 2002; 324(7345): 1053

62. Check E. US panel recommends 'black box' warnings for antidepressants. Nat Med 2004; 10(10): 1005

63. Cheung A, Sacks D, Dewa CS et al. Pediatric prescribing practices and the FDA Black-box warning on antidepressants. J Dev Behav Pediatr 2008; 29(3): 213-5

64. Cluxton RJ Jr, Li Z, Heaton PC, et al. Impact of regulatory labeling for troglitazone and rosiglitazone on hepatic enzyme monitoring compliance: Findings from the state of Ohio medicaid program. Pharmacoepidemiol Drug Saf 2005; 14(1): 1-9

65. Cockey C.D. Ephedra banned. AWHONN Lifelines 2004; 8(1): 19-25.

66. Corry M, Bonner G, McEntee S et al. Hospitals do not inform GPs about medication that should be monitored. Fam Pract. 2000; 17(3): 268-71

67. Cotter, J. and E. Wooltorton. New restrictions on celecoxib (Celebrex) use and the withdrawal of valdecoxib (Bextra). CMAJ 2005; 172(10): 1299

68. Crawford CL. Licensing thalidomide in Australia. Med J Aust 2004; 180(4): 199-200

69. Cuzzell JZ. FDA approves mandatory risk management program for isotretinoin. Dermatol Nurs 2005; 17(5): 383

70. Dahl M and Sjöqvist F. Pharmacogenetic Methods as a Complement to Therapeutic Monitoring of Antidepressants and Neuroleptics. Ther Drug Monit 2000; 22(1): 114-7

71. Edwards IR. Withdrawing drugs: nefazodone, the start of the latest saga. Lancet 2003; 361(9365): 1240

72. Ensom M, Chang T, and Patel P. Pharmacogenetics The Therapeutic Drug Monitoring of the Future? Clin Pharmacokinet 200; 40(11): 783-802.

73. Feldstein AC, Smith DH, Perrin N et al. Improved therapeutic monitoring with several interventions: a randomized trial. Arch Intern Med 2006; 166(17): 1848-54.

74. Feltelius N. and Lindblad S. New drugs require nw follow-up surveillance. Lakartidningen 2001; 98(9): 951-3.

75. Frances C Hoizey G, Millart H et al., Methylphenidate (Ritalin) use in France. Therapie 2002; 57(2): 189-193

76. Frances C, Hoizey G, Millart H et al. Paediatric methylphenidate (Ritalin) restrictive conditions of prescription in France. Br J Clin Pharmacol. 2004; 57(1): 115-116

77. Franic DM and Pathak DS. Communicating the frequency of adverse drug reactions to female patients. Drug Inf J 2000; 34(1): 251-272

78. Franke HA, Woods DM, and Holl JL. High-alert medications in the pediatric intensive care unit. Pediatr Crit **Care** Med 2009; 10(1): 85-90

79. Fraunfelder FW. Twice-yearly exams unnecessary for patients taking quetiapine. Am J Ophthalmol 2004; 138(5): 870-1

80. Fuller DE, Hornfeldt CS, Kelloway JS et al, The Xyrem Risk Management Program. Drug Saf 2004; 27(5): 293-306.

81. Gale EA. Lessons from the glitazones: a story of drug development. Lancet 2001; 357(9271): 1870-5

82. Gebhart F. Calls mount for black box warning on fluoroquinolones. Drug Topics 2004; 148(7): 43

83. Gerlach M, Schulz E, and Fegert JM. "Therapeutic drug monitoring", a strategy for improving drug safety in child and adlescent psychiatry and psychotherapy. Z Kinder Jugendpsychiatr 2005; 33(3): 157-8

84. Gex-Fabry M, Balant-Gorgia A, and Balant L. Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. Ther Drug Monit 2003; 25: 46-53.

85. Graham DJ, Drinkard CR., Shatin D et al. Liver enzyme monitoring in patients treated with troglitazone. JAMA 2001; 286: 831-33.

86. Grenier N, LebelV, Gill M et al. Nursing support program to decrease or prevent side effects of pegylated liposomal doxorubicin (PLD) in patients with recurrent epithelial ovarian cancer (REOC). Proc Am Soc Clin Oncol 2005; 23 (No 16S, Part I of II) 8198

87. Griffin J.P. Prepulsid withdrawn from UK & US markets. AdverseDrug React Toxicol Rev 2000; 19(3): 177

88. Guo JJ, Curkendall S, Jones JK et al. Impact of cisapride label changes on codispensing of contraindicated medications. Pharmacoepidemiol Drug Saf 2003; 12(4): 295-301

89. Habib AS and Gan TJ. The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia. J Clin Anesth 2008; 20(1): 35-39

90. Hetland ML, Unkerskov J, Ravn T et al., Routine database registration of biological therapy increases the reporting of adverse events twentyfold in clinical practice. First results from the Danish Database (DANBIO). Scand J Rheumatol. 2005; 34(1): 40-4.

91. Horowitz BZ, Bizovi K, and Moreno R. Droperidol--behind the black box warning. Acad Emerg Med 2002; 9(6): 615-8.

92. Hugman B. From the Uppsala monitoring centre: a review of viewpoint part 1 and part 2. Drug Saf 2005; 28(7): 645-6

93. Jacoby JL, Fulton J, Cesta M et al., After the black box warning: dramatic changes in ED use of droperidol. Am J Emerg Med. 2005; 23(2): 196

94. Jennings HR, Miller EC, Williams TS et al. Reducing anticoagulant medication adverse events and avoidable patient harm. Jt Comm J Qual Patient Saf 2008; 34(4): 196-200

95. Jones JK, Fife D, Curkendall S et al., Coprescribing and Codispensing of Cisapride and Contraindicated Drugs. JAMA 2001; 286(13): 1607-9

96. Jones MC. Update on isotretinoin and the iPLEDGE system 2007; Pharm. 32(4): 38-46

97. Katz LY, Kozyrskyj AL, Prior HJ et al., Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. CMAJ 2008; 178(8): 1005-1011

98. Kesselheim A.S. Fischer MA, and Avorn J. The rise and fall of Natrecor for congestive heart failure: implications for drug policy. Health Aff 2006; 25(4): 1095-102

99. Kilborn MJ. and RLWoosley. Registry for torsades de pointes with drug treatment exists. BMJ 2001; 322(7287): 672-3

100. Kivlahan C, Sangster W, Nelson K et al. Developing a Comprehensive Electronic Adverse Event Reporting System in an Academic Health Center. Jt Comm J Qual Improv 2002; 28(11): 583–94

101. Kurian BT, Ray WA, Arbogast PG et al., Effect of regulatory warnings on antidepressant prescribing for children and adolescents. Arch Pediatr Adolesc Med 2007; 161(7): 690-696

102. LaPointe NM, Weinfurt KP et al. Practitioner Acceptance of the Dofetilide Risk Management Program. Pharmacotherapy 2002; 22(8): 1041-6

103. Lasser KE, Seger DL, Yu DT et al., Adherence to Black Box Warnings for Prescription Medications in Outpatients. Arch Intern Med. 2006; 166: 338-44

104. Laugharne J, Davies A, Arcelus J et al., Informing patients about tardive dyskinesia: A survey of clinicians' attitudes in three countries. Int J Law Psychiatry. 2004; 27(1): 101-8

105. Lederer J, and Best D. Reduction in anticoagulation-related adverse drug events using a trigger-based methodology. Jt Comm J Qual **Patient** Saf 2005; 31(6): 313-8

106. Lee, LY, Kortepeter CM, Willy ME et al. Drug-risk communication to pharmacists: Assessing the impact of risk-minimization strategies on the practice of pharmacy. J Am Pharm Assoc 2008; 48: 494–500

107. Libby AM, Brent DA, Morrato EH et al. Decline in Treatment of Pediatric Depression After FDA Advisory on Risk of Suicidality with SSRIs. Am J Psychiatry 2007; 164: 884–891.

108. Locatelli F, Del Vecchio L and Pozzoni P. Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports. Perit Dial Int 2007; 27 Suppl 2: S303-7

109. Tarmina JD. Lenalidomide: A New Agent for Patients With Relapsed or Refractory Multiple Myeloma.

110. Lundmark J, Meier J, Cunningham F et al., Therapeutic drug monitoring of selective serotonin reuptake inhibitors influences clinical dosing strategies and reduces drug costs in depressed elderly patients. Acta Psychiatr Scand 2000; 101: 354-9

111. Lundmark J, Reis M and Bengtsson F. Therapeutic Drug Monitoring of Sertraline: Variability Factors as Displayed in a Clinical Setting. Ther Drug Monit 2000. 22(4): 446-454

112. Magnus D, Rodgers S and Avery AJ.GPs' views on computerized drug interaction alerts:questionnaire survey. J Clin Pharm Ther 2002; 27: 377–382

113. Maguire R, Miller M, Sage M et al. Results of a UK based pilot study of a mobile phone based advanced symptom management system (ASyMS) in the remote monitoring of chemotherapy related toxicity. Clin Eff Nurs 2005; 9: 202-210

114. Mallal S, Phillips E, Carosi G et al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med 2008; 358: 568-79

115. Masand PS, Schwartz TL, Wang X et al. Prescribing conventional antipsychotics in the era of novel antipsychotics: informed consent issues. American Journal of Therapeutics 2002; 9(6): 484-7

116. Mazor K, Andrade SE, Auger J et al., Communicating safety information to physicians:an examination of dear doctor letters. Pharmacoepidemiol Drug Saf 2005; 14: 869–875

117. McCann L, Maguire R, Miller M, et al. Patients' perceptions and experiences of using a mobile phone-based advanced symptom management system (ASyMS) to monitor and manage chemotherapy related toxicity. Eur J Cancer Care (Engl). 2009; 18(2): 156-64

118. McKoy J, Stonecash RE, Cournoyer D et al. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion 2008; 48: 1754-1762

119. Melnikow J, Paterniti D, Azari R et al. Preferences of Women Evaluating Risks of Tamoxifen (POWER) Study of Preferences for Tamoxifen for Breast Cancer Risk Reduction. Cancer 2005; 103(10): 996-2005

120. Morrato EH and Staffa JA. Effectiveness of risk management plans: a case study of pemoline using pharmacy claims data. Pharmacoepidemiol Drug Saf 2007; 16(1): 104-12

121. Morrison P, Meehan T, Gaskill D et al. Enhancing case managers' skills in the assessment and management of antipsychotic medication side-effects. Aust N Z J Psychiatry. 2000; 34(5): 814-21

122. Muller MJ, Dragicevic A, Fric M et al., Therapeutic Drug Monitoring of Tricyclic Antidepressants: How Does it Work under Clinical Conditions? Pharmacopsychiatry 2003; 36(3): 98-104

123. Muller MJ, Regenbogen B, Härtter S et al., Therapeutic drug monitoring for optimizing amisulpride therapy in patients with schizophrenia. J Psychiatr Res 2007; 41(8): 673-9

124. Munzenberger PJ and Montejo JM. Safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. Pharmacotherapy 2007. 27(7): 1020-8

125. Murray MD, Ritchey ME, Wu J et al., Effect of a pharmacist on adverse drug events and medication errors in outpatients with cardiovascular disease. [Erratum appears in Arch Intern Med 2009 Jul 13;169(13):1184]. Arch Intern Med 2009; 169(8): 757-63

126. Naso AR. Optimizing patient safety by preventing combined use of intramuscular olanzapine and parenteral benzodiazepines. Am J Health Syst Pharm 2008; 65(12): 1180-1183

127. Newman TB. A black-box warning for antidepressants in children? NEJM 2004; 351(16): 1595-8

128. Nordstrom B, Luo W, Fraeman K et al. Use of erythropoiesis-stimulating agents among chemotherapy patients with hemoglobin exceeding 12 grams per deciliter. J Manag Care Pharm. 2008; 14(9): 858-869

129. Nuttall GA, Eckerman KM, Jacob KA et al. Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? Anesthesiology 2007; 107:531–6.

130. Offit P.Withdrawal of rotavirus vaccine in the USA. Vaccines: Children and Practice 2000; 3(1): 2-3.

131. Oppenheimer J. and Aaronson D. Impact of recent black box warnings in the allergy world. Ann **AllergyAsthma** Immunol 2007; 99(4): 364-366.

132. Prins JM and Koopmans RP. [Novel side effects of moxifloxacin: making a balanced decision again]. Ned Tijdschr Geneeskd 2008; 152(34): 1862-4.

133. Prinz JC. [The EMEA suspends approval of Raptiva for psoriasis. Commentary]. Hautarzt 2009; 60(4): 345-6.

134. Pugashetti R. and Koo J. Efalizumab discontinuation: a practical strategy. J Dermatolog Treat 2009; 20(3): 132-6.

135. Recupero PR and Rainey SE. Managing risk when considering the use of atypical antipsychotics for elderly patients with dementia-related psychosis. J Psychiatr Pract 2007; 13(3): 143-152.

136. Richardson LP, Lewis CW, Casey-Goldstein M et al. Pediatric primary care providers and adolescent depression: a qualitative study of barriers to treatment and the effect of the black box warning. J Adolesc Health. 2007; 40(5): 433-9.

137. Richins C. Regulation of smoking cessation drugs by the Food and Drug Administration. FoodDrug Law J 2009; 64(2): 277-90.

138. Rosack J. New Data Show Declines In Antidepressant Prescribing. Psychiatr News 2005; 40 (17): 1.

139. Sanfelix-Gimeno G, Cervera-Casino P, Peiró S et al., Effectiveness of safety warnings in atypical antipsychotic drugs: an interrupted time-series analysis in Spain. Drug Saf 2009; 32(11): 1075-87.

140. Schachter DC and Kleinman I. Psychiatrists' attitudes about and informed consent practices for antipsychotics and tardive dyskinesia. Psychiatr Serv 2004; 55(6): 714-7.

141. Schussel K. and Schulz M. Prescribing of COX-2 inhibitors in Germany after safety warnings and market withdrawals. Pharmazie 2006; 61(10): 878-886.

142. Schwetz BA. New measures to manage risks associated with accutane. JAMA 2001; 285.

143. Segal ES, Valette C, Oster L et al., Risk management strategies in the postmarketing period: Safety experience with the US and European bosentan surveillance programmes. Drug Saf 2005; 28(11): 971-980.

144. Shatin D, Gardner JS, Stergachis A et al. Impact of mailed warning to prescribers on the co-prescription of tramadol and antidepressants. Pharmacoepidemiol Drug Saf 2005; 14: 149–154.

145. Sheridan C. Tysabri back on market. Nat Biotechnol; 2006. 24 (8).

146. Silman A, Klareskog L, Breedveld F et al. Proposal to establish a register for the long term surveillance of adverse events in patients with rheumatic diseases exposed to biological agents: the EULAR Surveillance Register for Biological Compounds. Ann Rheum Dis 2000; 59(6): 419-20.

147. Singer J.W. Cardiac toxicity of arsenic trioxide. Blood 2001; 98(5): 1633; author reply 1633-4.

148. Singh AK. The FDA black box for EPO: what should nephrologists do? Nephrol NewsIssues 2007; 21(6): 55-6.

149. Smalley W, Shatin D, Wysowski DK et al. Contraindicated use of cisapride: impact of food and drug administration regulatory action. JAMA 2000; 284(23): 3036-9.

150. Spalding BJ. Changes for ESAs. NaT Biotechnol 2008; 26(5): 483.

151. Spry L. The FDA, stocks, black boxes and ESAs. Nephrol NewsIssues 2007; 21(6): 53-4.

152. Starner CI, Schafer JA, Heaton AH et al., Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Manag Care Pharm 2008; 14(6): 523-531.

153. Tanne JH. FDA places “black box” warning on antidiabetes drugs. BMJ 2007; 334(7606): 1237.

154. Thompson CA. Bosentan enters market with risk management program. Am J Health Syst Pharm 2002; 59(6): 506.

155. Traynor K. Close vote by FDA advisers favors propoxyphene withdrawal. Am J Health Syst Pharm 2009; 66(6): 518-20.

156. Uhl K, Cox E, Rogan R et al. Thalidomde use in the US: experience with pregnancy testing in the S.T.E.P.S.1 programme. Drug Saf 2006; 29(4): 321–329.

157. Valente S, Murray L, and Fisher D. Nurses improve medication safety with medication allergy and adverse drug reports. J Nurs **Care** Qual 2007; 22(4): 322-7.

158. Van Geffen, Kruijtbosch M, Egberts AC et al. Patients' perceptions of information received at the start of selective serotonin-reuptake inhibitor treatment: Implications for community pharmacy. Ann Pharmacother 2009; 43(4): 642-649.

159. Vitello B and Swedo S. Antidepressant Medications in Children. N Engl J Med, 2004. 350(15): 1489-1491.

160. von Moos R, Thuerlimann BJ, Aapro M et al., Pegylated liposomal doxorubicin-associated hand-foot syndrome: recommendations of an international panel of experts. Eur J **Cancer** 2008; 44(6): 781-90.

161. Watkins P. COMT inhibitors and liver toxicity. Neurology 2000; 55(11): Supplement 4.

162. Weatherby LB, Nordstrom BL, Fife D et al., The impact of wording in "Dear doctor" letters and in black box labels. Clin Pharmacol Ther. 2002; 72(6): 735-42.

163. Weatherby LB, Walker AM, Fife D et al. Contraindicated medications dispensed with cisapride: Temporal trends in relation to the sending of 'Dear Doctor' letters. Pharmacoepidemiol Drug Saf 2001; 10(3): 211-218.

164. Wechsler J. Advisory committee prompts FDA to consider black box warning for ADHD drugs. Formulary 2006; 41(3): 114.

165. Wilkinson JJ, Force RW, and Cady PS. Impact of safety warnings on drug utilization: marketplace life span of cisapride and troglitazone. Pharmacotherapy 2004; 24(8): 978-86.

166. Wolf DV. Suicidality following black-box warning [1]. J Am Acad Child Adolesc Psychiatry 2005; 44(5): 405.

167. Wright M. Tell patients about yellow card reporting. Pharmaceutical Journal 2008; 280(7489): 174.

168. Wysowski D, Nourjah P, and Swartz L. Bleeding Complications With Warfarin Use: A Prevalent Adverse Effect Resulting in Regulatory Action. Arch Intern Med 2007; 167(13): 1414-1419.

169. Yetzer E, Blake K, Goetsch N et al. Medication safety series: take charge! Rehabil Nurs 2009; 34(5): 195-9.

Table I. Literature Review Distribution of RMIs by Country across Pre and Post-guidance Periods

Country	N(%) 2000-2004	N(%) 2005-2009	TOTAL N (%)	Chi square p-value (pre vs. post guidances)
USA	25 (46.3)	40(61.5)	65(54.6)	0.09[i]
EU	10(18.5)	12(18.5)	22(18.5)	0.99
INTL	3(5.6)	6(9.2)	9(7.6)	0.51*[i]
AUS	3(5.6)	0(0.0)	3(2.5)	0.09*[d]
CAN	2(3.7)	0(0.0)	2(1.7)	0.20*[d]
SGP	1(1.8)	0(0.0)	1(0.8)	0.45*[d]
UNK	10(18.5)	7(10.8)	17(14.3)	0.23[d]
TOTAL	54(100.0)	65(100.0)	119(100.0)	

Country Codes as per ISO 3166:

USA=United States of America; AUS=Australia; CAN=Canada; SGP=Singapore

European Union member states

INTL =International (more than one region)

UNK = Unknown / unspecified

* Fisher Test

i = Increased proportion in post-guidances period

d = Decreased proportion in post-guidances period

Table II: Literature Review: Overall Distribution of RMI Type

RMI		N (% of Education Material	% of Total RMIs
Education Material		37(100.0)	31.0
	Patient / Public safety warning	17(45.9)	14.3
	HCP safety warning	10(27.0)	8.4
	DHCP Letter	6(16.2)	5.0
	Medication Guide	3(8.1)	2.5
	Warning with unspecified target audience	1(2.7)	0.8
Black box warning		22	18.5
TDM		11	9.2
Education program		9	7.6
Restricted distribution		8	6.7
Informed consent		6	5.0
Withdrawals		8	6.7
Patient registry		4	3.4
Pregnancy registry		1	0.8
Pharmacogenetics		2	1.7
Black Triangle Symbol		3	2.5
Patient alert card		1	0.8
Other		7	6.0
TOTAL		119	100.0

Table III. Literature Review: RMI Distribution per RMI Target Population

Population	2000-2004 N (% of Pre-guidances RMIs)	2005-2009 N (% of Post-guidances RMIs)	TOTAL N (% of Total RMIs)	Chi square p-value (pre vs. post guidances)
Pediatric	4(7.4)	6(9.2)	10(8.4)	1.00*[i]
Adults	0(0.0)	1(1.5)	1(0.8)	1.00*[i]
Women	7(13.0)	4(6.2)	11(9.2)	0.22*[d]
Men	0(0.0)	1(1.5)	1(0.8)	1.00*[i]
Geriatric	1(1.8)	2(3.1)	3(2.5)	1.00*[i]
All	38(70.4)	49(75.4)	87(73.1.0)	0.54[i]
Unknown	4(7.4)	2(3.1)	6(5.0)	0.41* [d]
TOTAL	54(100.0)	65(100.0)	119(100.0)	

* Fisher Test

i = Increased proportion in post-guidances period

d = Decreased proportion in post-guidances period

Table IV. Website Review: Distribution of RMIs by Region

Region	2000-2004 N (%)	2005-2009 N (%)	TOTAL	Chi square p-value (pre vs. post guidances)
TGA (AUS)	7 (2.1)	11 (1.4)	18 (1.6)	0.38[d]
PMDA (JPN)	24 (7.4)	91 (11.6)	115 (10.3)	0.04 [i]
EU (MHRA + EMA)	37 (11.3)	146 (18.6)	183 (16.5)	0.003 [i]
Health Canada (CAN)	131 (40.2)	127 (16.1)	258 (23.2)	<0.001[d]
FDA (USA)	127 (39.0)	411 (52.3)	538 (48.4)	<0.001 [i]
TOTAL	326 (100.0)	786 (100.0)	1112 (100.0)	

TGA = Therapeutic Goods Administration; AUS = Australia; PMDA = Pharmaceutical and Medical Devices Agency; JPN = Japan; MHRA = Medicines and Healthcare Products Regulatory Agency;

GBR = United Kingdom; EU = European Union; EMA = European Medicines Agency; CAN = Canada; FDA = Food and Drugs Administration; USA = United States of America

i = Increased proportion in post-guidances period

d = Decreased proportion in post-guidances period

Table V: Website Review: Overall Distribution of RMI Type

RMI Type	N (%)
Education Material	956 (86.0)
Black box warning	45 (4.0)
Withdrawals	39 (3.5)
Therapeutic Drug Monitoring	19 (1.7)
Restricted distribution	16(1.4)
Registry	14 (1.3)
Patient Alert Card	9 (0.8)
Education program	12 (1.1)
Informed Consent	2 (0.2)
TOTAL	1112 (100.0)

Figure I. Literature Review: Source Identification Flow Chart

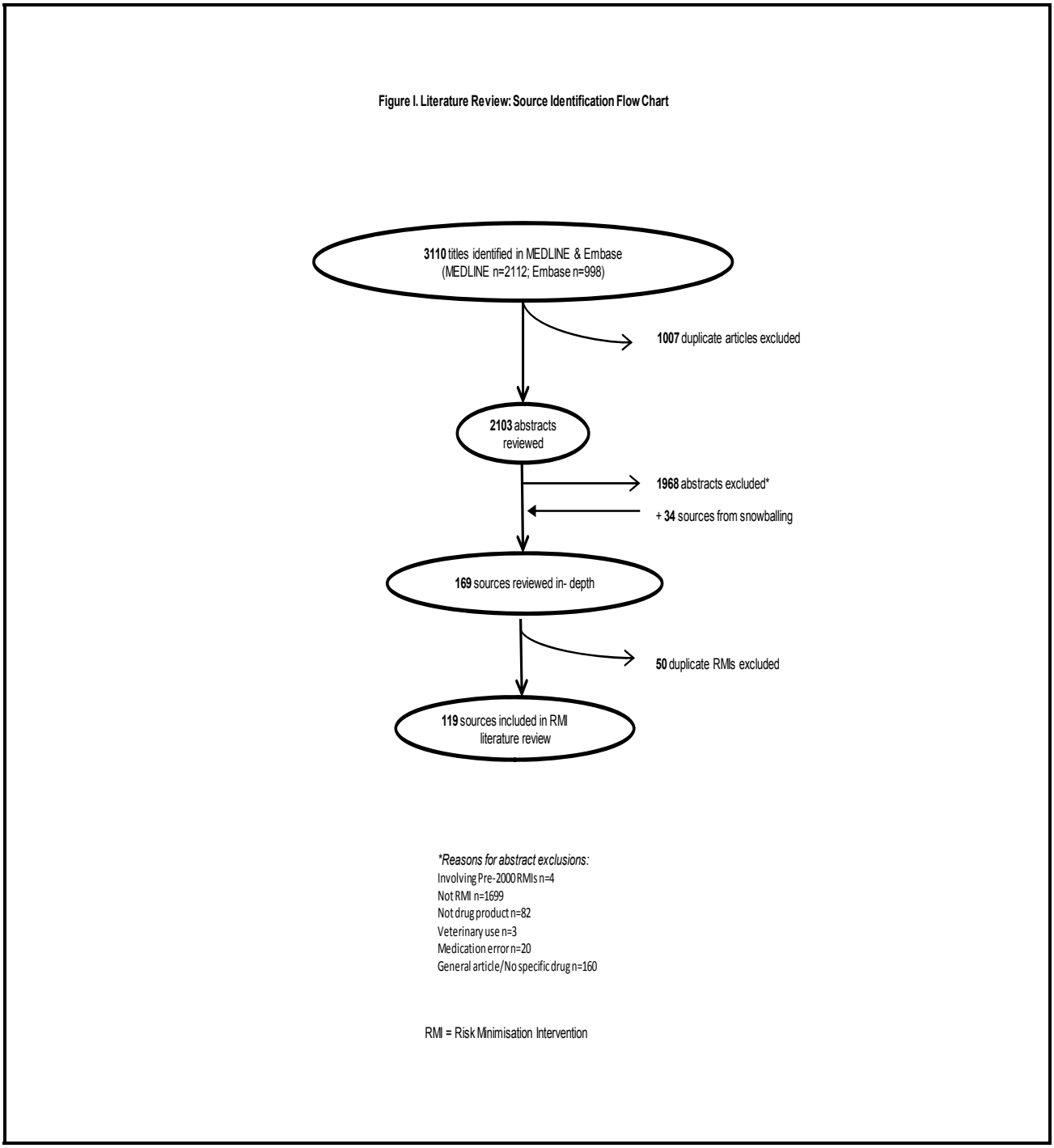
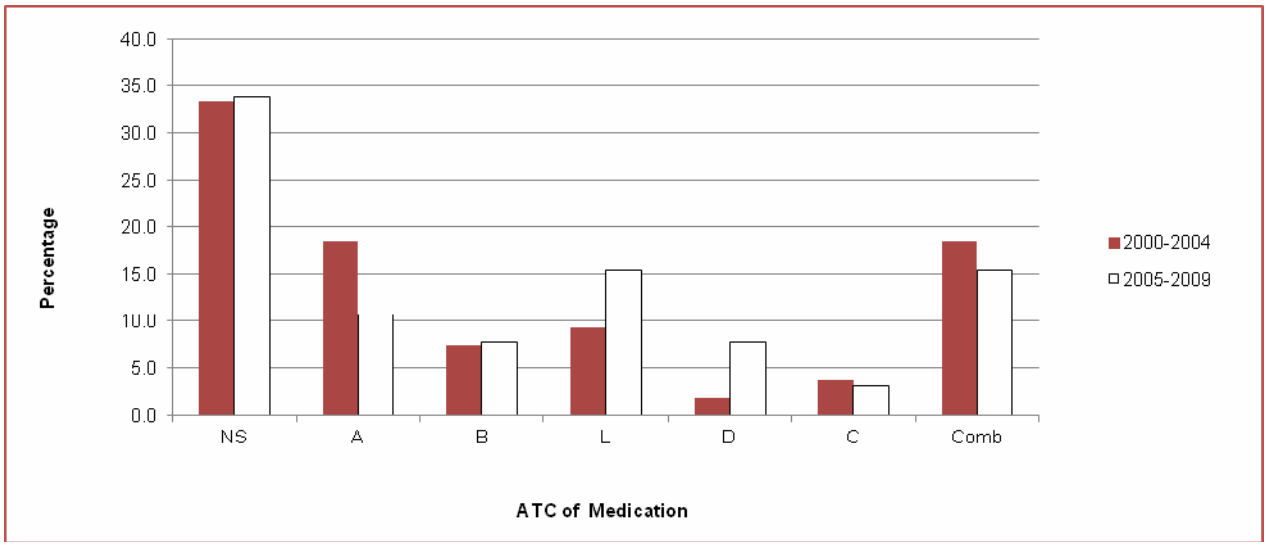


Figure II. Literature Review: Distribution of RMIs by Drug Anatomical Therapeutic Chemical (ATC) Classification

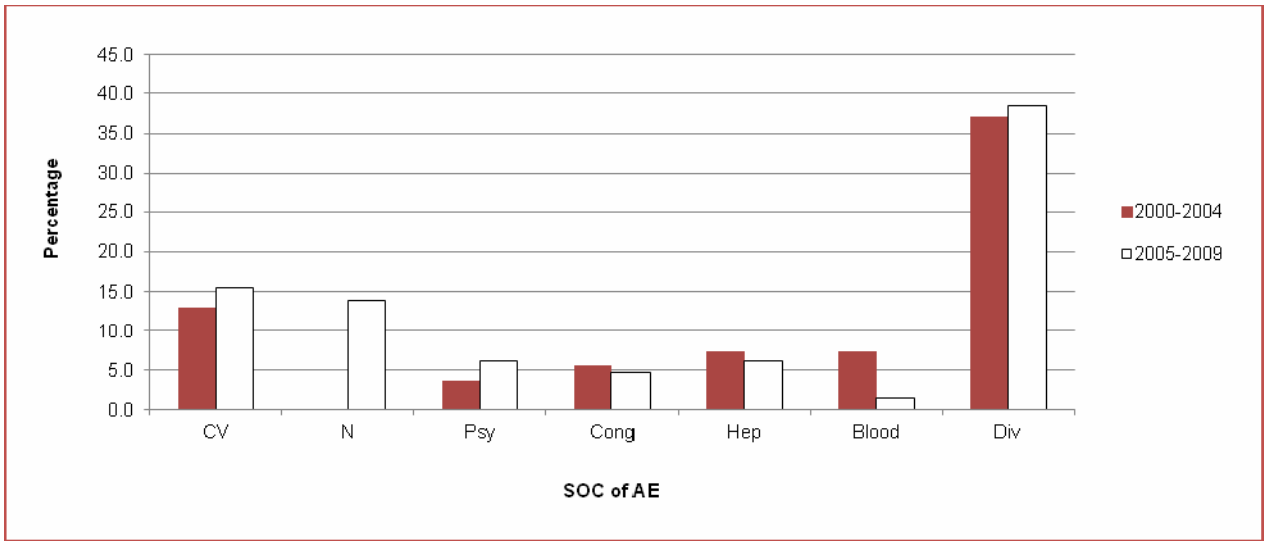


NS = Nervous System; A = Alimentary tract and metabolism; B = Blood and blood forming organs; L = Antineoplastic and immunomodulating agents;

D = Dermatologicals; C=Cardiovascular system

Comb = Combination

Figure III. Literature Review: Distribution of RMIs by Adverse Event System Organ Class (AE SOC, MedDRA Terminology)



SOC as per MedDRA: CV=Cardiovascular disorder; N=Neoplasms, benign, malignant and unspecified; Psy=Psychiatric disorders; Con= Congenital, familial, and genetic disorders; Hep=Hepatobiliary disorders; Blood = Blood and lymphatic system disorders

Div= Diverse (combination of AE SOC)

Figure IV. Website Review: RMI Identification Flow Chart_

Appendix I – Literature Review Data Extraction Table

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
1	2000	Corry et al [66]	Hospitals do not inform GPs about medication that should be monitored.	GBR	EU	Various - requiring regular monitoring	Diverse	Diverse	EM – Commun ica-tion	All
2	2000	Franic et al [77]	Communicating the frequency of adverse drug reactions to female patients.	USA	USA	Various	Diverse	Diverse	EM – Commun ica-tion	Women
3	2000	Griffin et al [87]	Prepulsid withdrawn from UK & US markets.	GBR / USA	INTL - 2UK / USA	cisapride	Alimentary tract and metabolism	Cardiac Disorder s	Withdra wal	All
4	2000	Morrison et al [121]	Enhancing case managers' skills in the assessment and management of antipsychotic medication side-effects.	AUS	AUS	Various	Nervous System	Diverse	Educatio n Program	All
5	2000	Offit et al [130]	Withdrawal of rotavirus	USA	USA	Rotavirus	Various -	GI	Withdra	Pediatri

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			vaccine in the USA.			Vaccine	vaccine	Disorders	wal	c
6	2000	Silman et al [146]	Proposal to establish a register for the long term surveillance of adverse events in patients with rheumatic diseases exposed to biological agents: the EULAR Surveillance Register for Biological Compounds.	GBR	EU-SWE/NLD/UK	Biologicals	Antineoplastic and immunomodulating agents	Diverse	Patient Registry	All
7	2000	Smalley et al [149]	Contraindicated use of cisapride: impact of food and drug administration regulatory action.	USA	USA	cisapride	Alimentary tract and metabolism	Cardiac Disorders	EM – Communica-tion	All
8	2000	Watkins et al [161]	COMT inhibitors and liver toxicity.	USA	INTL - 3USA/EU/CAN	tolcapone/ entacapone	Nervous System	Hepato-biliary Disorders	BBW	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
9	2000	FDA website [1]	Food and Drug Administration. FDA talk paper: Janssen Pharmaceutica stops marketing cisapride in the US.	USA	USA	cisapride	Alimentary tract and metabolism	Cardiac Disorders	RD	All
10	2000	Dahl et al [70]	Pharmacogenetic methods as a complement to therapeutic monitoring of antidepressants and neuroleptics	SWE	Not indicated	Various	Nervous System	Diverse	Pharmac o-genetics	All
11	2000	Lundmark et al [111]	Therapeutic drug monitor of selective serotonin reuptake inhibitors influences clinical dosing strategies and reduces drug costs in depressed elderly patients.	SWE	EU	SSRI's	Nervous System	Diverse	TDM	Geriatric

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
12	2000	Lundmark et al [110]	Therapeutic drug monitoring of sertraline: variability factors as displayed in a clinical setting.	SWE	Not indicated	sertraline	Nervous System	Diverse	TDM	All
13	2000	Lotronex.com website [2]	Prescribing program for Lotronex. Pharmacist information.	USA	USA	alosetron	Alimentary tract and metabolism	GI Disorders	Withdrawal	Women
14	2000	Celgene.com website [3]	Celgene. S.T.E.P.S. prevention and protection.	USA	USA	thalidomide	Antineoplastic and immunomodulating agents	Congenital, familial and genetic disorders	RD / Education Program	Women
15	2001	Not indicated [4]	Failings in treatment advice, SPCs and black triangles.	GBR	Not indicated	Various	Diverse	Diverse	Black Triangle Symbol	Unk
16	2001	Not indicated [5]	Black-box' warning and letter are insufficient to protect patients, study	USA	Not indicated	Various	Diverse	Diverse	BBW	Unk

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			finds.							
17	2001	Bourke et al [55]	Joint charts in drug handling. Toward increased drug safety.	DNK	Not indicated	Various	Diverse	Drug Interacti on	Other	Unk
18	2001	Brown et al [57]	The incidence and reporting of adverse drug reactions in the Division of Psychiatry.	GBR	EU	Various	Diverse	Diverse	Black Triangle Symbol	All
19	2001	Feltelius et al [74]	New drugs require new follow-up surveillance.	SWE	Not indicated	TNF-blockers	Antineoplastic and immunomodula ting agents	Diverse	Other	All
20	2001	Kilborn et al [99]	Registry for torsades de pointes with drug treatment exists.	USA	Not indicated	Various	Diverse	Diverse	Patient Registry	All
21	2001	Singer et al [147]	Cardiac toxicity of arsenic trioxide.	USA	USA	arsenic trioxide	Antineoplastic and immunomodula ting agents	Cardiac Disorder s	BBW	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
22	2001	Graham et al [85]	Liver enzyme monitoring in patients treated with troglitazone.	USA	USA	trioglitazone	Alimentary tract and metabolism	Hepato-biliary Disorders	TDM / EM-HCP Commun ica-tion	All
23	2001	Schwetz [142]	New measures to manage risks associated with accutane.	USA	USA	isotretinoin	Dermatologicals	Congenital, familial and genetic disorders	IC / EM-Medication Guide	Women
24	2001	Ensom et al [72]	Pharmacogenetics- The therapeutic drug monitoring of the future?	CAN	INTL	Various	Diverse	Diverse	Pharmac o-genetics	All
25	2002	Thompson [154]	Bosentan enters market with risk management program.	USA	USA	bosentan	CV system	Hepato-biliary Disorders	RD/ patient registry / Medication Guide	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
26	2002	Charatan [61]	FDA advisory panels recommend Lotronex be put back on market.	USA	USA	alosetron HCl	Alimentary tract and metabolism	GI Disorders	EM - Medication guide	Women
27	2002	Frances et al [75]	Methylphenidate (Ritalin) use in France. [French].	FRA	EU	methylphenidate	Nervous System	Combination-Not specified	RD / Restricted Prescription	Pediatric
28	2002	Horowitz et al [91]	Droperidol--behind the black box warning.	USA	USA	droperidol	Alimentary tract and metabolism	Cardiac Disorders	BBW	All
29	2002	Masand et al [115]	Prescribing conventional antipsychotics in the era of novel antipsychotics: informed consent issues.	USA	USA	Various	Nervous System	Diverse	IC	All
30	2002	Magnus et al [112]	GPs' views on computerized drug interaction alerts: questionnaire survey.	GBR	EU	Various	Diverse	Drug Interaction	Other	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
31	2002	Singapore H S A website [36]	HSA product safety alert. Update on Eprex and pure red cell aplasia.	SGP	SGP	HSA (ESA)	Blood and blood forming organs	Blood and Lymphatic system disorders	EM – Communica-tion	All
32	2002	Australia TGA website [37]	Epoetin alfa and pure red cell aplasia. Australian adverse drug reactions bulletin.	AUS	AUS	epoietin	Blood and blood forming organs	Blood and Lymphatic system disorders	EM – Communica-tion	All
33	2002	France AFSSPS website [7]	Agence Francaise de Securite Sanitaire des Produits de Sante, les lettre aux prescripteurs, Eprex®: information importante de pharmacovigilance. 17	FRA	EU	epoietin	Blood and blood forming organs	Blood and Lymphatic system disorders	EM – Communica-tion	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			December 2002							
34	2002	Health Canada website [11]	Important safety information—EPREXTM (epoetin alfa)—Janssen-Ortho Inc. Health Canada. 26 November 2001	CAN	CAN	epoietin	Blood and blood forming organs	Blood and Lymphatic system disorders	EM – Communica-tion	All
35	2002	FDA website [13]	Danco Laboratories. Open letter to health care providers (Apr. 19, 2002). (Dear doctor letter)	USA	USA	mifespristone	Genitourinary system and sex hormones	Pregnancy, puerperium etc.	EM – Communica-tion	Women
36	2002	Kivlahan et al [100]	Developing a comprehensive electronic adverse event reporting system in an academic health center.	USA	USA	Various	Diverse	Diverse	Other	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
37	2003	Not indicated [16]	Patients to have new role in improving methotrexate safety says NPSA.	GBR	Not indicated	methotrexate	Alimentary tract and metabolism	Unknown	Black Triangle Symbol	All
38	2003	Edwards [71]	Withdrawing drugs: nefazodone the start of the latest saga.	SWE	EU	nefazodone	Nervous System	Hepato-biliary Disorders	Withdrawal	All
39	2003	LaPointe et al [49]	Evaluation of the dofetilide risk-management program.	USA	USA	dofetilide	CV system	Cardiac Disorders	RD / Education	All
40	2003	Not indicated [15]	Suicide risk warning for children now extended by CSM to cover venlafaxine.	GBR	Not indicated	venlafaxine	Nervous System	Psychiatric disorders	EM – Communica-tion	Pediatric
41	2003	Muller et al [122]	Therapeutic drug monitioring of tricyclic antidepressants: how does it work under clinical conditions?	DEU	USA	trycyclic anti-depressants	Nervous System	Diverse	TDM	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
42	2003	Fosamax.com website [17]	Merck. Paget's patient support program.	USA	USA	alendronate sodium	Alimentary tract and metabolism	Diverse	Education Program	Women
43	2004	Not indicated [18]	Paroxetine review makes safety warnings.	GBR	Not indicated	paroxetine	Nervous System	Unknown	EM – Communica-tion	Unk
44	2004	Check [62]	US panel recommends 'black box' warnings for antidepressants.	USA	USA	Various	Nervous System	Psychiatric disorders	BBW	Pediatric
45	2004	Cockey [65]	Ephedra banned.	USA	USA	ephedrine	Alimentary tract and metabolism	Cardiac Disorders	Withdrawal	All
46	2004	Crawford [68]	Licensing thalidomide in Australia.	AUS	AUS	thalidomide	Antineoplastic and immunomodulating agents	Congenital, familial and genetic disorders	RD /Physician registry / Patient registry/ Education	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
47	2004	Fraunfelder [79]	Twice-yearly exams unnecessary for patients taking quetiapine.	USA	USA	quetiapine	Nervous System	Endocrine Disorders	TDM	All
48	2004	Gebhart [82]	Calls mount for black box warning on fluoroquinolones.	USA	USA	Fluoroquino-lones	Antiinfective for systemic use	Metabo-lism and nutrition disorders	BBW	All
49	2004	Laugharne [104]	Informing patients about tardive dyskinesia: A survey of clinicians' attitudes in three countries.	AUS	EU	Various	Nervous System	Nervous System disorder	IC / TDM for at risk patients	All
50	2004	Schachter et al [140]	Psychiatrists' attitudes about and informed consent practices for antipsychotics and tardive dyskinesia.	CAN	CAN	Various	Nervous System	Nervous System disorder	IC	All
51	2004	FDA website [19]	US Food and Drug Administration: 2004	USA	USA	olanzapine	Nervous System	Metabo-lism and	EM – Commun	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			Safety Alert: Zyprexa (olanzapine)					nutrition disorders	ica-tion	
52	2004	Calhoun et al [59]	Challenges to the FDA approval of mifepristone.	USA	USA	mifespristone	Genitourinary system and sex hormones	Unknown	EM – Commun ica-tion	All
53	2004	Baumann et al [51]	Therapeutic monitoring of psychotropic drugs - An outline of the AGNP-TDM expert group consensus guideline.	CHE	EU	Psychotropic drugs	Nervous System	Diverse	TDM	All
54	2004	Fuller et al [80]	The Xyrem risk management program.	USA	USA	sodium oxybate (GHB)	Nervous System	Diverse	RD	All
55	2005	Not indicated [20]	Calcineurin inhibitors: Black box warning for pimecrolimus and tacrolimus. [German].	DEU	Not indicated	pimecrolimus / tacrolimus	Antineoplastic and immunomodulating agents	Neoplasms	BBW	All
56	2005	Not indicated [21]	FDA advisory committees recommend	USA	USA	COX inhibitors	Nervous System	Cardiac Disorder	BBW	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			marketing of COX-2 inhibitors with 'black box' warning.					s		
57	2005	Not indicated [22]	Impotence drugs receive blindness warning.	USA	USA	tadalafil/ vardenafil/ sidenafil	CV system	Eye Disorder s	EM – Commun ica-tion	Men
58	2005	Not indicated [23]	Stronger warnings needed for asthma treatments.	USA	USA	fluticasone propionate /salmeterol / formoterol / salmeterol	Respiratory system	GI Disorder s	BBW	All
59	2005	FDA website [26]	Food and Drug Administration, "2005 Safety Alert: Natrecor (nesiritide)," 13 July 2005.	USA	USA	nesiritide	CV system	Renal and urinary disorder s	EM – Commun ica-tion	All
60	2005	Melnikow et al [119]	Preferences of Women Evaluating Risks of Tamoxifen (POWER)	USA	USA	tamoxifen	Antineoplastic and immunomodula	Diverse	Educatio n Program	Women

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			study of preferences for tamoxifen for breast cancer risk reduction.				ting agents			
61	2005	Baumann et al [52]	The AGNP-TDM Expert Group Consensus Guidelines: focus on therapeutic monitoring of antidepressants.	CHE	EU	Various	Nervous System	Diverse	TDM	All
62	2005	Beltrani [53]	The "black boxing" of protopic and elidel.	USA	USA	tacrolimus / pimecrolimus	Dermatologicals	Neoplasms	BBW	Pediatric
63	2005	Bensouda-Grimaldi et al [54]	Isotretinoin: compliance with recommendations in childbearing women.	FRA	EU	isotretinon	Dermatologicals	Congenital, familial and genetic disorders	IC / Medication Guide	Women

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
64	2005	Gerlach et al [83]	"Therapeutic drug monitoring" a strategy for improving drug safety in child and adolescent psychiatry and psychotherapy.	DEU	Not indicated	Various	Nervous System	Diverse	TDM	Pediatri c
65	2005	Hetland et al [90]	Routine database registration of biological therapy increases the reporting of adverse events twentyfold in clinical practice. First results from the Danish Database (DANBIO).	DNK	EU	Biological s	Antineoplastic and immunomodula ting agents	Diverse	Patient Registry	All
66	2005	Hugman [92]	From the Uppsala monitoring centre: a review of viewpoint part 1 and part 2.	SWE	INTL - ALL - Who members	Various	Diverse	Diverse	EM – Commun ica-tion	All
67	2005	Lederer et al [105]	Reduction in anticoagulation-related	USA	USA	warfarin	Blood and blood forming	Diverse	Other - Trigger -	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			adverse drug events using a trigger-based methodology.				organs		based method	
68	2005	Shatin et al [144]	Impact of mailed warning to prescribers on the co-prescription of tramadol and antidepressants.	USA	USA	tramadol	Nervous System	Cardiac Disorders	EM – Communica-tion	All
69	2005	Cotter et al [67]	New restrictions on celecoxib (Celebrex) use and the withdrawal of valdecoxib (Bextra).	CAN	INTL-CAN/US	celecoxib	Nervous System	Cardiac Disorders	EM – Communica-tion	All
70	2005	FDA website [28]	Dear Health Care Provider letter. Important drug warning and new information for Clozaril (clozapine). Novartis Pharmaceuticals Corporation, December	USA	USA	clozapine	Nervous System	Diverse	EM – Communica-tion	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			2005.							
71	2005	FDA website [33]	FDA, "FDA Public Health Advisory: Suicidality in Adults Being Treated with Antidepressant Medications" 30 June 2005.	USA	USA	Various	Nervous System	Psychiatric disorders	EM – Communica-tion	Adults
72	2005	FDA website [29]	US Food and Drug Administration: FDA Public Health Advisory: Deaths with antipsychotics in elderly patients with behavioral disturbances, April 11, 2005, accessed January 30, 2006.	USA	USA	Various	Nervous System	Unknown	EM – Communica-tion	Geriatric
73	2005	Not indicated [24]	European COX-2 review recommends new warnings.	GBR	EU	COX inhibitors	Nervous System	Cardiac Disorders	EM – Communica-tion	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
74	2005	Not indicated [31]	The Food and Drug Administration. Public Health Advisory: suicidal thinking in children and adolescents being treated with Strattera (atomoxetine). 29 September 2005.	USA	USA	atomexitine	Nervous System	Psychiatric disorders	EM – Communica-tion	Pediatric
75	2005	Grenieret al [86]	Nursing support program to decrease or prevent side effects of pegylated liposomal doxorubicin (PLD) in patients with recurrent epithelial ovarian cancer (REOC).	CAN	Not indicated	doxorubicin	Antineoplastic and immunomodulating agents	Diverse	Education Program	All
76	2005	Mazor et al [116]	Communicating safety inforamtion to physicians: an examination of Dear Dr. Letters.	USA	USA	Various	Diverse	Diverse	EM – Communica-tion	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
77	2006	Aaronson [48]	The "black box" warning and allergy drugs.	USA	USA	Various	Alimentary tract and metabolism	Diverse	BBW	All
78	2006	Feldstein et al [73]	Improved therapeutic monitoring with several interventions: a randomized trial.	USA	USA	Various	Diverse	Diverse	TDM	All
79	2006	Schussel et al [141]	Prescribing of COX-2 inhibitors in Germany after safety warnings and market withdrawals.	DEU	EU	COX inhibitiors	Nervous System	Cardiac Disorders	EM – Commun ica-tion	All
80	2006	Sheridan [145]	Tysabri back on market.	USA	USA	natalizumab	Antineoplastic and immunomodulating agents	Neoplasms	Patient Registry	All
81	2006	Wechsler [164]	Advisory committee prompts FDA to consider black box warning for ADHD drugs.	USA	USA	Amphetamine-based drugs for ADHD, such as Adderall	Nervous System	Cardiac Disorders	BBW	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
						and Dexedrine				
82	2006	Lasser et al [103]	Adherence to black box warnings for prescription medications in outpatients	USA	USA	Various	Diverse	Diverse	BBW	All
83	2006	FDA website [34]	Medication Guide: Coumadin tablets (warfarin sodium tablets, USP) crystalline. 2006.	USA	USA	warfarin	Blood and blood forming organs	Diverse	EM - Medicati on guide	Unk
84	2007	Jones [96]	Update on isotretinoin and the iPLEDGE system.	USA	Not indicated	isotretinoi n	Dermatological s	Congeni tal, familial and genetic disorder s	Patient registries / Pharmaci st registries Physician registries - Pregnanc	Women

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
									y	
85	2007	Morrato et al [120]	Effectiveness of risk management plans: a case study of pemoline using pharmacy claims data.	USA	USA	pemoline	Nervous System	Hepato-biliary Disorders	BBW	All - Mainly Pediatric
86	2007	Muller et al [123]	Therapeutic drug monitoring for optimizing amisulpride therapy in patients with schizophrenia.	DEU	EU	amisulpride	Nervous System	Diverse	TDM	All
87	2007	Munzenberger et al [124]	Safety of topical calcineurin inhibitors for the treatment of atopic dermatitis.	USA	USA	topical calcineurin inhibitors	Antineoplastic and immunomodulating agents	Neoplasms	EM - Medication Guide/ Black Box Warning	All
88	2007	Oppenheimer et al [131]	Impact of recent black box warnings in the allergy world.	USA	USA	long-acting - agonists	Alimentary tract and metabolism	Neoplasms	BBW	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
						(LABAs) and calcineurin inhibitors				
89	2007	Recupero et al [135]	Managing risk when considering the use of atypical antipsychotics for elderly patients with dementia-related psychosis.	USA	USA	Various	Nervous System	Cardiac Disorders	BBW	Geriatric
90	2007	Singh [148]	The FDA black box for EPO: what should nephrologists do?	USA	USA	epoietin	Blood and blood forming organs	Neoplasms	BBW	All
91	2007	Valente et al [157]	Nurses improve medication safety with medication allergy and adverse drug reports.	USA	Not indicated	Various	Diverse	Diverse	Education Program	All
92	2007	Wysowski et al [168]	Bleeding complications with warfarin use: A prevalent adverse effect resulting in regulatory	USA	USA	warfarin	Blood and blood forming organs	Blood and Lympha tic	BBW	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			action.					system disorders		
93	2007	Tanne [153]	FDA places "black box" warning on antidiabetes drugs.	USA	USA	Various	Alimentary tract and metabolism	Cardiac Disorders	BBW	All
94	2007	FDA website [35]	The Food and Drug Administration.FDA proposes new warnings about suicidal thinking, behavior in young adults who take antidepressant medications. 2 May 2007.	USA	USA	Various	Nervous System	Psychiatric disorders	BBW	Pediatric
95	2008	FDA webite [47]	FDA ALERT - Simvastatin Used With Amiodarone.	USA	USA	simvtatin& amiodarone	Alimentary tract and metabolism/ CV	Musculoskeletal	EM – Communica-tion	All
96	2008	Not indicated [39]	Tegaserod: withdrawal from the world market.	FRA	INTL	tegaserod	Alimentary tract and	Cardiac Disorder	Withdrawal	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			A treatment for constipation with cardiovascular adverse effects.				metabolism	s		
97	2008	Castaneda et al [60]	RevAssist: A comprehensive risk minimization programme for preventing fetal exposure to lenalidomide.	USA	USA	lenalidomide	Antineoplastic and immunomodulating agents	Congenital, familial and genetic disorders	RD	Women
98	2008	Mallal et al [114]	HLA-B*5701 Screening for Hypersensitivity to Abacavir.	AUS	INTL	abacavir	Antiinfective for systemic use	Immune system disorders	TDM-Pharmaco-genomics	All
99	2008	Jennings et al [94]	Reducing anticoagulant medication adverse vents and avoidable patient harm.	USA	USA	Anticoagulant	Blood and blood forming organs	Diverse	Education Program / TDM	All
100	2008	Naso [126]	Optimizing patient safety by preventing	USA	USA	olanzapine	Nervous System	Drug Interacti	Other	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			combined use of intramuscular olanzapine and parenteral benzodiazepines.					on		
101	2008	FDA website [43]	Suicidality and antiepileptic drugs: FDA alert.	USA	USA	Various	Nervous System	Psychiat ric disorder s	EM – Commun ica-tion	All
102	2008	von Moos et al [160]	Pegylated liposomal doxorubicin-associated hand-foot syndrome: recommendations of an international panel of experts.	CHE	INTL	doxorubici n	Antineoplastic and immunomodula ting agents	Metabo-lism and nutrition disorder s	Educatio n Program	All
103	2008	Wright [167]	Tell patients about yellow card reporting.	GBR	EU	Various	Diverse	Diverse	Patient alert card	Unk
104	2008	UK MHRA website [42]	MHRA Drug Safety Update on Exenatide .	GBR	EU	exenatide	Alimentary tract and metabolism	Hepato-biliary Disorder s	EM – Commun ica-tion	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
105	2008	FDA website [6]	Tumor necrosis factor-alpha blockers (TNF blockers), Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab) Sept 2008.	USA	USA	Various	Antineoplastic and immunomodulating agents	Neoplasms	EM – Communica-tion	All
106	2008	Prinset al [132]	Novel side effects of moxifloxacin: making a balanced decision again.	NLD	Not indicated	moxifloxacin	Antiinfective for systemic use	Hepato-biliary Disorders	EM – Communica-tion	All
107	2008	FDA website [46]	Information on exenatide (marketed as Byetta®).	USA	USA	exenatide	Alimentary tract and metabolism	Hepato-biliary Disorders	EM – Communica-tion	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
108	2008	Lee et al [106]	Drug-risk communication to pharmacists: Assessing the impact of risk-minimization strategies on the practice of pharmacy.	USA	USA	Various	Diverse	Diverse	EM – Commun ica-tion / Medicati on Guides	All
109	2009	Franke et al [78]	High-alert medications in the pediatric intensive care unit.	USA	USA	Various	Diverse	Diverse	EM – Commun ica-tion	Pediatri c
110	2009	McCann et al [117]	Patients' perceptions and experiences of using a mobile phone-based advanced symptom management system (ASyMS) to monitor and manage chemotherapy related	GBR	EU	Various	Antineoplastic and immunomodula ting agents	Metabo-lism and nutrition disorder s	Other	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			toxicity.							
111	2009	Murray et al [125]	Effect of a pharmacist on adverse drug events and medication errors in outpatients with cardiovascular disease.	USA	USA	Various	Diverse	Diverse	Educatio n Program	All
112	2009	Prinz [133]	The EMEA suspends approval of Raptiva for psoriasis. Commentary.	DEU	EU	efalizumab	Dermatological s	Neoplas ms	Withdra wal	All
113	2009	Pugashetti et al [134]	Efalizumab discontinuation: a practical strategy.	USA	INTL	efalizumab	Dermatological s	Neoplas ms	Withdra wal	All
114	2009	Richins [137]	Regulation of smoking cessation drugs by the Food and Drug	USA	USA	varenicline , buproprion	Nervous System	Diverse	BBW	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			Administration.							
115	2009	Sanfelix-Gimeno et al [139]	Effectiveness of safety warnings in atypical antipsychotic drugs: an interrupted time-series analysis in Spain.	ESP	EU	olanzapine and risperidone	Nervous System	Diverse	EM - Commun ication / Prior authorisa -tion policy	All
116	2009	Traynor [155]	Close vote by FDA advisers favors propoxyphene withdrawal.	USA	USA	propoxy-phene	Nervous System	Cardiac Disorder s	BBW	All
117	2009	Van Geffen et al [158]	Patients' perceptions of information received at the start of selective serotonin-reuptake inhibitor treatment:	NLD	EU	SSRI inhibitors	Nervous System	Diverse	IC	All

	Year	Authors [Lit Review Source Ref #]	Title	Country of publica-tion	Region of imple-ment as per article	Product active ingredient	Therapeutic Area	AE - SOC	Inter-vention Type	Patient Popu-lation
			Implications for community pharmacy.							
118	2009	Yetzer et al [169]	Medication safety series: take charge!	USA	Not indicated	Various	Diverse	Diverse	Educatio n Program	All
119	2009	Hitt, E [46]	Botulinum Toxin Safety Warnings Updated and Name Changes Issued	USA	USA	botulinum toxin	Musculoskeleta l system	Diverse	EM – Commun ica-tion	All

Chapter 6. Thesis Discussion

This thesis studied some of the methodologies used in two main areas of therapeutic risk management.

1) *Risk detection,* through the review of data mining methodologies, a review of databases used to perform data mining, and finally through the conduct of a data mining demonstration study in the Quebec health claims databases.

2) *Risk minimisation*, through a systematic review of RMI characteristics in the literature and among regulatory agency websites.

For each sub-study, advantages and limitations are discussed in further detail in the "Discussion" sections of each of Chapters 4 and 5 of the thesis, respectively. However, a brief summary is provided here, followed by a view of the contributions these studies bring to the global risk management forum.

Data mining study discussion summary

This study being the first data mining study to be conducted in a Canadian health claims database poses a new development. Further, the fact that it is analyzing a denominator-based methodology also contributes to its uniqueness. Using the administrative database

avoids the common signal detection challenges of SR databases of underreporting and reporting bias. It also has the potential for future analysis of signal verification and confirmation since claims databases are a major tool for risk evaluation studies, i.e. hypothesis-testing studies. Controlling for overall health status using the CDS has never before been attempted in a published data mining study. Accounting for the depletion of susceptible effect through a time window sensitivity analysis is also a new approach not considered in previous studies.

Conversely, this study was not able to detect very rare AEs due to the low statistical power. The main reason being that only a random sample of approximately 10% of the elderly population was available. Even the entire population of elderly may be insufficient to detect rare AEs, a fact that has demonstrated by a large international European consortium[64]. Control of confounding was performed on age, sex, and overall health status. However only a basic, less refined control of the covariate of age was permitted because of its classification in 5-year intervals. This constraint, imposed by the database custodian, is a limitation of the study.

However, the data mining analysis was still able to reveal important gaps in the data mining and signal detection processes. Most prior data mining studies have been conducted in SR databases, with the aid of denominator–independent methodology, few studies have been

applied to administrative claims databases using denominator-dependent methods, and none such studies have occurred in Canada or within a Canadian health claims database. Data mining and signal detection are conducted by few organisations in Canada. These are important gaps in the data mining and signal detection processes which we addressed through the application of the MaxSPRT data mining tool to a Canadian claims database, the RAMQ.

With the data mining study, future research with this methodology could involve application of the method to the RAMQ database, in a real-time manner using newly marketed drugs provided the RAMQ database is updated regularly. However, this may prove a challenge because of current access constraints. Due to excessive timelines and restrictive conditions for access, it does not appear feasible to obtain prospective data slices on a quarterly basis. As for any drug surveillance process in Canada, potential future real-time implementation would be greatly dependent on the timely availability of the claims databases. This could pose a challenge for use globally as many databases may not be accessible regularly even though in practice they are populated in real-time.

This data mining study was merely a demonstration study as there are many possible additions that can be made to the process that was outlined. Possibly accounting for time to onset of AE, or residual risk periods after exposure in order to further reduce the false positive signals in instances where the AEs of interest have previously been identified.

Testing a potential solution for analysing rare AEs such as using proxies of less severe symptoms of the disease. Use of the database for the subsequent phase in signal detection, i.e. verification / confirmation of the signal, is also a potential next step with the RAMQ database because it contains much information on potential confounders such as concomitant medications.

Global data mining discussion

Over the last eight years, there has been a debate concerning the usefulness of claims databases for signal detection processes [28,144]. Although the use of spontaneous databases for signal detection is quite extensive (since 1998 [74]), only three published studies were located that used an administrative claims database as of 2007 [30,32,63,] . Our study showed that for one drug-AE pair (rosiglitazone-acute MI), the Quebec claims database is in fact feasible for the application of at least one data mining algorithm: the MaxSPRT. However, the feasibility of using the database depends on the accuracy of the AE diagnostic codes (in this case ICD-9 codes), as well as the size of the database and statistical power. The RAMQ database holds a maximum of 800 000 patients. The cohort used for this study constituted about 11% of the entire database (87, 389). However, this cohort was large enough to detect a signal in only one of the drug-AE pairs, the rosiglitazone-acute MI pair This pair possessed a cumulative total of 52,906 patient months of exposure to rosiglitazone for the initial follow-up period of 3months,and 90,941 patient months for the

6month follow-up period. Despite elimination of prevalent acute MI cases through the exclusion of ICD-9 codes related to ER visits, the AE was frequent enough to produce a signal (a cumulative total of 118 events for the 3 month time period, RR at signal =1.26; and a cumulative total of 151 events for the 6month time period, RR at signal =1.18).

The case studies that were restricted to female patients (rosiglitazone and pioglitazone and risk of increased fractures in female patients) however did not possess enough power to detect a signal. Their cumulative patient exposure were 3,064 and 1,731 patient months respectively for their 3 month follow-up time periods, less than one-tenth that of the rosiglitazone acute MI case study. While the cumulative number of AEs for the 3-month time period were 12 and 6, respectively. The RR at the points of their respective Health Canada warnings were 1.24 and 0.72, respectively. Furthermore, the rosuvastatin-rhabdomyolysis group did not exhibit enough occurrences of the AE to be analysed using the method (a cumulative total of only 9 events for the entire 10-year time period of the data). Based on the literature, the prevalence of rhabdomyolysis among rosuvastatin users is 6.59% [145] . Thus, anticipated number of events for the number of rosuvastatin users in the database (14,583) was 961. The low number of rhabdomyolysis cases actually observed shows that the tool should be used for events that are better coded and have a higher incidence (as was discussed earlier with the event of acute MI).

The validity of the comparator drugs is also a subject of debate. As with previous data mining studies [31,63] , comparator drugs used for the same indication as the study drug were

selected for the analysis in order to control for indication bias. However, it was challenging to find a comparator drug that had the same or similar life cycle as the study medication. In most cases, the comparator drug had been on the market for many more years than the study drug which may have led to variations in factors of patterns of use by the population such as: changes in the drug's indication, contraindications, and reimbursable status over time, unmeasured prescription channelling, which could account for potential variances in AE occurrences over time, despite adjustments for age, sex, and overall health status.

Accuracy of diagnostic codes present in physician billings databases has also been a subject of debate, which may also hamper the validity of data mining. Diagnostic codes in hospitalization databases have been shown to be more accurate but, in Canada, these databases are not available in real-time; hence would not be suitable for implementation in a prospective safety surveillance study.

Also because of the lag times between approval and reimbursement in public drug programs, the ability to cover the entire population on a timely basis is limited and consequently the statistical power of any study using the available data will be reduced.

In real-world prospective signal detection, one may generate a very large number of false positive signals. This is a well-documented fact in signal detection and shall remain a barrier to the use of data mining [146,147]. However, we have demonstrated that the CDS

which has been used extensively in pharmacoepidemiologic studies, is also suitable and can be an important addition to the overall field of pharmacovigilance.

Risk minimisation review discussion

The systematic review of RMIs was accepted for publication in Drug Safety and also a unique study in that there are no other publications that previously summarised RMIs from such a variety of sources, and over such a lengthy time period. Nor had any publications attempted to analyse the effect of regulatory guidances on the RMIs. Because it analysed RMIs across regions, it is in fact a globally-relevant project that can be beneficial for various members of the pharmaceutical, regulatory, and academic world.

Although it is a good amalgamation of data on RMIs, there may be additional RMIs that were not included in the study due to inconsistencies in website data availability, the fact that only certain regulatory websites were searched (e.g. all websites consulted were in the English language) could restrict the inclusiveness of this review. In addition, the specific classification system used in this review could lead to discrepancies and /or constraints of the review results. Finally, the sources available for review possessed insufficient data on methods. However, information such as this is not likely to be published and obtaining it would in all probability involve a qualitative survey of pharmaceutical companies. Due to

confidentiality and proprietary matters, this would most likely pose an obstacle and little feedback would be expected as a result.

The issue of publication bias is also a factor as only more complex RMIs would be expected to be published in the literature. The majority of these would be those studies and / or evaluations of such that are implemented by researchers, as opposed to the pharmaceutical companies. Consequently, it is difficult to say how comprehensive this RMI review actually was.

Despite the challenges involved in the systematic review, a realm of useful information was still proficiently collected and diverse gaps were identified in the process.

With the RMI review, future perspectives include the continued review of RMIs going forward to increase the reserve of information obtained from this analysis. Studies to identify the methods as well as methodological challenges related to the assessment of RMI effectiveness can be undertaken in order to comply with the guidances on risk management. Determining which are the most effective of the RMIs based on the results of observed studies, and which are the most convenient methods to be used with the various types of RMIs. Also, a more comprehensive website search, including other non-English speaking countries could also be performed.

Chapter 7. Thesis Conclusion

The data mining study showed that the RAMQ databases are indeed conducive to quantitative signal detection although the method may need to be refined for each drug-AE pair individually in order to improve its performance.

The RMI review found that the guidances on therapeutic risk management appeared to result in an important increase in the number of RMIs implemented within the USA, EU and Japan. It is also beneficial in in helping authors of risk management plans determine which risks are focused on in risk management plans. E.g. the fact that the major AE SOC classes of RMIs were those of the nervous system could serve as a trigger for pharmaceutical companies to look into the necessity of a RMI when faced with a similar AE.

Although both of these separate studies: the data mining study, and the RMI systematic review, at first glance may appear to be separate entities, they do both fit under the common umbrella of therapeutic risk management, namely risk detection, and risk minimisation respectively. Examining these two areas of risk management (as opposed to risk evaluation, or risk communication) was chosen because it was observed that these are the two domains that are lacking in general knowledge as well as methodological advances. On the contrary, the areas of risk evaluation and risk communication have been in place for very many years. E.g. Pharmacoepidemiology has been used for over 20 years in order to evaluate

risks associated with medications[148,149]. As such it was deemed more relevant to focus on these two "hot-topic" subjects of the field of risk management as there is indeed the need for new research in these areas [35,150,151].

This thesis addresses the specific areas that were lacking in risk management and it is believed to have brought contributions of methodological nature to the data mining processes such as the depletion of susceptibles effect, and control of prescription channelling through overall health status. In addition, the effect of regulatory guidances in risk minimisation as well as the identification of gaps in RMI implementation was also performed.

From a global perspective, attempts at using claims databases for signal detection are few and far between. Studies from only three research teams were located that were conducted in the US, EU, and Korea. In the future, more countries should explore the possibility of making use of health claims databases as a resource for drug safety signal detection.

The observed effect of the depletion of susceptible at delaying a signal was quite profound in our study. The process was also relatively simple to implement. If other data mining groups would apply the time window sensitivity analysis in order to control for this effect, there should be even earlier signal detection possibilities world-wide.

Generally with signal detection studies, the power of a study is determined by the available size of the database. In the instance of this data mining study, the cohort obtained from the Quebec database was found to be too small to detect a signal for three out of the four drug-AE pairs. Future possibilities to address this could be the allowance of a higher proportion of the RAMQ database for research.

The small database size could also be addressed by a potential project to merge databases across provinces (such as is the case in countries such as Denmark [152]). This would create a larger resource of data for research. Indeed this would be a tedious and time-consuming task that would raise both confidentiality concerns and some politics, however in Europe, there is currently an ongoing initiative to create a central spontaneous database for all EU member states, i.e. EudraVigilance [153]. Considering this project, an attempt at combining perhaps two of the databases in Canada, perhaps Ontario and Saskatchewan, for the conduct of research does not seem vastly unreasonable.

With regards to risk minimisation on a global scale, more regulatory agencies could create specific websites or pages with risk minimisation interventions or risk management plans outlined. This would serve as a more accessible resource for risk management-specific information. Of the sites included in the systematic review, only the FDA and the EMA had dedicated pages to approved risk management plans.

In addition, further systematic reviews encompassing websites of additional regulatory agencies of individual countries can be undertaken in order to obtain more information and be more comprehensive.

Overall, the findings made within the field of therapeutic risk management from this thesis are expected to be used to provide additional information supporting signal detection; provide new guidance on data mining; help improve RMI execution, and improve drug safety surveillance and therapeutic risk management within the Canadian population and world-wide.

Bibliography

1 Daemmrich A, and Krucken G. Risk versus risk: decision-making dilemmas of drug regulation in the United States and Germany. Sci Cult (Lond). 2000; 9(4):505-34

2 Lenz W, Knapp K. Thalidomide Embryopathy. Arch Environ Health. 1962; 5:100-5

3 McBride WG. Thalidomide and congenital abnormalities. The Lancet 2 1961: 1358

4 Lawson DH. Pharmacovigilance in the 1990s. Br J Clin Pharmacol 1997; 44: 109–110

5 CIOMS Working Group VIII Report “Practical Aspects of Signal Detection in Pharmacovigilance". Geneva, CIOMS, 2010; p.15

6 Merck Sharp & Dohme (MSD) Announces Voluntary Worldwide Withdrawal of VIOXX® (rofecoxib) Merck Frosst Canada Ltd. [Online]. Available from URL: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2004/vioxx_2_ltp-lp-eng.php. [Accessed 2012 February 10]

7 Dabu-Bondoc S, Franco S. Risk-Benefit Perspective sin Cox-2 Blockade. Curr Drug Saf.3 (1) 14-23(10)

8 Hinz B, Renner B, AND Brune K. Drug Insight: cyclo-oxygenase-2 inhibitors—a critical appraisal. Nat Clin Pract Rheumatol. 2007 Oct;3(10):552-60

9 European Medicines Agency. Guideline on Risk Management Systems for Medical Products for Human Use. [online] Available from URL: http://www.ema.europa.eu/pdfs/human/phv/11590605en.pdf. [Accessed 2010 April 11]

10 U.S. Food and Drug Administration. Guidance for Industry Development and Use of Risk Minimization Action Plans [online]. Available from URL: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf. [Accessed 2010 October 1]

11 Code of Federal Regulations(CFR) 21. Title 21, Volume 5. Food and Drug Administration Department of health and Human Services. Subchapter D. Drugs for Human Use. Part 312 Investigational New Drug Application. [online]. Available from URL: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=312

12 Bennett C, Adams J, Knox K, et al. Clinical trials: Are they a good buy? J Clin Oncol. 2001;19:4330-4339.

13 Trontell A. Expecting the Unexpected – Drug Safety, Pharmacovigilance, and the Prepared Mind. N Eng J Med. 2004; 351:1385-87

14 van der Heijden, van Puijenbroek EP, van Buuren S. On the assessment of adverse drug reactions from spontaneous reporting systems: the influence of under-reporting on odds ratios. Stat Med. 2002; 21:2027–2044.

15 Emmendorfer T, Glassman PA, Moore V et al. Monitoring adverse drug reactions across a nationwide health care system using information technology. Am J Health Syst Pharm. 2012; 69(4):321-8

16 World Health Organization (WHO), Uppsala Monitoring Centre. The use of the WHO-UMC system for standardized case causality assessment. WHO [online]. Available from URL: who-umc.org/Graphics/24734.pdf [Accessed 2012 Jan 08]

17 Agbabiaka TB, Savovij, and Ernst E. Methods for Causality Assessment of Adverse Drug Reactions A Systematic Review. Drug Saf 2008; 31 (1): 21-37

18 Tubert T, Begaud B, Pere J-C et al. Power and weakness of spontaneous reporting: A probabilistic approach. J Clin Epidemiol.1992; 45(3): 283-286

19 Tubert P, Begaud B, Haramburu F, et al. Spontaneous reporting: how many cases are required to trigger a warning? Br J Clin Pharmacol. 1991; 32: 407-8

20 Lexchin J. Drug withdrawals from the Canadian market for safety reasons, 1963-2004. CMAJ 2005;172(6):765-7.

21 Wysowski DK, Swartz L. Adverse Drug Event Surveillance and Drug Withdrawals in the United States, 1969-2002 The Importance of Reporting Suspected Reaction. Arch Intern Med. 2005;165:1363-1369

22 Bakke OM, Wardell WM, Lasagna L. Drug discontinuations in the United Kingdom and the United States, 1964 to 1983: issues of safety. Clin Pharmacol Ther. 1984; 35:559-567

23 Fung M, Thornton A, Mybeck K, Wu JH, Hornbuckle K, Muniz E. Evaluation the characteristics of safety withdrawal of prescription drugs from worldwide pharmaceutical markets: 1960 to 1999. Drug Inf J. 2001;35:293-317.

24 Additions to the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness–FDA: proposed rules. Fed Regist. 2000; 65:256-257

25 List of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness–FDA: proposed rule. Fed Regist. 1998;63: 54082-54089.

26 Strom BL (ed). Pharmacoepeidemiology (Fourth Edition). Sussex: John Wiley, 2005.

27 Graham DJ, Mosholder AD, Gelperin K et al. Pharmacoepidemiology and Risk Management. Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA. (Ch 33). In Pharmacoepidemiology. Fourth Edition. Sussex: John Wiley, 2005.

28 Almenoff JS, Pattishall EN, Gibbs TG. Novel Statistical Tools for Monitoring the Safety of Marketed Drugs. Clin Pharmacol Ther. 2007 ; 82 (2) : 157-66

29 Canada Vigilance Program—Collecting and Assessing Adverse Reaction Reports. [online] Available at URL: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/pubs/medeff/fs-if/2011-cvp-pcv/2011-cvp-pcv-eng.pdf. [Accessed 2012 Jan 10]

30 Choi N-K, Chang Y, Cho YK et al. Signal detection of rosuvastatin compared to other statins: data-mining study using national health insurance claims database. Pharmacoepidemiol Drug Saf. 2010; 19: 238–246

31 Brown JS, Kulldorff M, Petronis KR. Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations. Pharmacoepidemiol Drug Saf. 2009; 18(3):226-34.

32 Trifiro G, Patadia V, Coloma PM et al. Comparison of Signal detection using healthcare database network vs. Spontaneous reporting system database : the EU-ADR experience. Abstract from 2011 ISOP; Drug Saf. 2011; 34(10): 990-991

33 Moride Y and Metge C. Data sources to support research on real world drug safety & effectiveness in Canada: An environmental scan & evaluation of existing data elements. [Online]. Available from www.pharmacoepi.ca. [Accessed 2012 January 4]

34 Choi NK, Hahn S, Park BJ. Increase in mortality rate following coprescription of cisapride and contraindicated drugs. Ann Pharmacother 2007; 41(4): 667–673.

35 Leiderman DB. Risk management of drug products and the U.S. Food and Drug Administration: Evolution and context. Drug and Alcohol Dependence 2009 ; 105S S9–S13

36 Hauben M, Aronson JK. Defining “signal” and subtypes in pharmacovigilance based on a systematic review of previous definitions . Drug Saf 2009; 32:1-12

37 Shakir SAW. Thoughts on Signal Detection in Pharmacovigilance. Drug Saf. 2007; 30 (7): 603-606

38 Hauben M, Madigan D, Gerritis CM et al. The role of data mining in Pharmacovigilance. Expert Opin. Drug Saf. (2005) 4(5):929-948

39 Dangoumau J, Evreux JC, Jouglard J. Method for determination of undesirable effects of drugs [in French]. Therapie 1978; 33:373-81

40 Jones JK. Adverse drug reactions in the community health setting: approaches to recognizing, counseling, and reporting. Fam Community Health 1982; 5: 58-67

41 Food and Drug Administration. Tysabri (natalizumab) Public Health Advisory [online] Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152733.htm. [Accessed 2012 February 12]

42 Lehman HP, Chen J, Gould AL. An Evaluation of Computer-Aided Disproportionality Analysis for Post-Marketing Signal Detection. Clin Pharmacol Ther. 2007; 82(2) 173-80

43 Moore N, Thiessard F and Begaud B. The history of disproportionality measures (reporting odds ratio, proportional reporting rates) in spontaneous reporting of adverse drug reactions. Pharmacoepidemiol Drug Saf, 2005; 14: 285–286

44 Hauben M and Zhou Xiaofeng. Quantitative Methods in Pharmacovigilance: focus on signal detection. Drug Saf 2003; 26 (3)

45 Almenoff J, Tonning J, Gould L et al. Perspectives on the Use of Data Mining in Pharmacovigilance. Drug Saf 2005; 28 (11): 981-1007

46 Van Manen RP, Fram D, DuMouchel W. Signal detection methodologies to support effective safety management. Expert Opin Drug Saf; 2007 6(4) 451-64

47 Bate A, Lindquist M, Edwards IR, Orre R. A data mining approach for signal detection and analysis. Drug Saf 2002; 25(6): 393–397.

48 Edwards IR, Lindquist M, Bate A. Data mining. In Pharmacovigilance, Mann RD, Andrews EB (eds). JohnWiley & Sons, Ltd: New York, 2002: 292–300.

49 Szarfman A, Machado, SG, O'Neil RT. Use of Screening Algorithms and Computer systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Saf. 2002; 25(6) 381-392

50 DuMouchel W, Pregibon D. Empirical Bayes Screening for Multi-Item Associations. AT&T Labs---Research 180 Park Avenue Florham Park, NJ 07932, USA. 2001

51 Lindquist M, Stahl M, Bate A, et al. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. Drug Saf. 2000; 23 (6): 533-42

52 Wayne D. Biostatistics: A Foundation for analysis in health sciences. 9th edition. Atlanta (GA).Wiley. 2009

53 Begaud B, Fourrier A. La comparaison des nombres attend et observe en pharmacovigilance: principe mise en oeuvre et applications. Bordeaux ARME Pharmacovigilance Editions . 1999

54 Wald A. Sequential Analysis. Wiley: New York, 1947.; Wald A. Sequential tests of statistical hypotheses. Ann Math Stat 1945; 16:117—186

55 Jennison C, Turnbull BW. Group Sequential Methods with Applications to Clinical Trials. Chapman & Hall, CRC: London, Boca Raton, 2000

56 Whitehead J. The Design and Analysis of Sequential Clinical Trials. Ellis Horwood: Chichester, 1983.

57 Kulldorff M, Davis RL, Kolczak M, Lewis E, Lieu T, Platt R. A maximized sequential probability ratio test for drug and vaccine safety surveillance. Technical Report, 2008. Available from: http://www.populationmedicine.org/content/docs/maxSPRTsubm.pdf.

58 Abt K. Poisson sequential sampling modified towards maximal safety in adverse event monitoring. Biometrical Journal. 1998; 40:21—41

59 Lingling L and Kulldorff M. A conditional maximized sequential probability ratio test for pharmacovigilance. Statistics in Medicine. Statist. Med. 2010 ; 29 284—295.

60 DuMouchel W. Bayesian Data Mining in Large Frequency Tables, With an Application to the FDA Spontaneous Reporting System. Am Stat. 1999 53(3) 177 - 193

61 van Puijenbroek EP, Bate A, Leufkens HG et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002;11(1):3-10

62 Nelson J, Cook A, Onchee Yu. Evaluation of signal detection methods for use in prospective postlicensure medical product safety surveillance. FDA Sentinel Initiative Safety Signal Identification contract (contract HHSF223200S31324P). Horsham (PA) 2009 Mar 31

63 Brown JS, Kulldorff M, Chan KA et al. Early detection of adverse drug events within population-based health networks: application of sequential testing methods. Pharmacoepidemiol Drug Saf, 2007; 16: 1275–1284

64 Trifiro G, Patadia V, Schuemie MJ. EU-ADR healthcare database network vs. spontaneous reporting system database: preliminary comparison of signal detection. Stud Health Technol Inform. 2011;166:25-30

65 Hazell L, Shakir SAW. Under-Reporting of Adverse Drug Reactions – A Systematic Review. Drug Saf. 2006; 29 (5): 385-396

66 Moride Y, Haramburu F, Requejo AA, et al. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol. 1997; 43: 177-81

67 Norén GN, Orre R, Bate A, IR E., Duplicate detection in adverse drug reaction surveillance. Data mining and Knowledge Discovery 2007; 14(3): 305–328.

68 Goldman S. Adverse event reporting and standardized medical terminologies: strengths and limitations. Drug Inf J. 2002; 36: 439–444

69 Brown EG. Effects of coding dictionary on signal generation: a consideration of use of MedDRA compared with WHO-ART. Drug Saf 2002;25(6):445-52.

70 Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999;20(2):109-17.

71 FAQ Vigibase Services. [Online]. Available from URL: http://www.umc-products.com/DynPage.aspx?id=73565&mn1=1107&mn2=1132&mn3=6051#17.%20May%20I%20publish%20the%20data%20from%20Vigibase? [Accessed 2012 January 12]

72 Lindquist M. Use of Triage Strategies in the WHO Signal-Detection Process. Drug Saf 2007; 30 (7): 635-637

73 Gavali DK, Kulkarni KS, Kumar A et al. Therapeutic class-specific signal detection of bradycardia associated with propranolol hydrochloride. Indian J Pharmacol 2009. 41(4) : 162-166.

74 Bate A, Lindquist M, Edwards IR et al. A Bayesian neural network method for adverse drug reaction signal generation.Eur J Clin Pharmacol. 1998 54(4):315-21.

75 Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001. 10(6):483-6.

76 Egberts AC, Meyboom RH, van Puijenbroek EP. Use of measures of disproportionality in pharmacovigilance: three Dutch examples. Drug Saf. 2002; 25 (6): 453-8

77 van Puijenbroek E, Diemont W, van Grootheest K. Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. Drug Saf. 2003;26(5):293-301.

78 Hauben M. Application of an empiric Bayesian data mining algorithm to reports of pancreatitis associated with atypical antipsychotics. Pharmacother. 2004; 24(9):1122-9.

79 Hauben M. Trimethoprim-induced hyperkalaemia - Lessons in data mining. Br J Clin Pharmacol. 2004; 58(3):338-9.

80 Schnell FM, Coop A. An evaluation of potential signals for ventricular arrhythmia and cardiac arrest with dolasetron, ondansetron, and granisetron in the FDA combined Spontaneous Reporting System/Adverse Event Reporting System. Current Therapeutic Resarch 2005. 66 (5) 409-19

81 Roux E, Thiessard F, Fourrier A et al. Spontaneous reporting system modelling for data mining methods evaluation in pharmacovigilance. IEEE Transactions On Information Technology In Biomedicine. 2005: 9(4)

82 Thiessard F, Fourrier A, Haramburu F. Comparaison de méthodes de génération automatique de signal pour la detection des effets indesirables des medicaments. Journées Francophones d'Informatique Médicale , Lille 12-13 mai 2005.

83 Conforti A, Magro L, Moretti U et al. Fluvastatin and hepatic reactions: A signal from spontaneous reporting in Italy. Drug Saf. 2006;29(12):1163-72.

84 Hochberg AM, Reisinger SJ, Pearson PK. Using data mining to predict safety actions from FDA adverse event reporting system data. Drug Inf J. 2007; 41: 633–643

85 Shalviri G, Mohammad K, Majdzadeh R et al. Applying quantitative methods for detecting new drug safety signals in pharmacovigilance national database. Pharmacoepidemiol Drug Saf. 2007 Oct;16(10):1136-40.

86 Hammond IW, Rich DS, Gibbs TG. Effect of consumer reporting on signal detection: Using disproportionality analysis. Expert Opin Drug Saf. 2007; 6(6):705-12.

87 Salvo F, Polimeni G, Cutroneo PM et al. Allergic reactions to oral drugs: A case/non-case study from an Italian spontaneous reporting database (GIF). Pharmacol Res. 2008; 58(3-4):202-7.

88 Li C, Xia J, Deng J et al. A Comparison of measures of disproportionality for signal detection on adverse drug reaction spontaneous reporting database of Guangdong province in China. Pharmacoepidemiol Drug Saf. 2008; 17(6):593-600

89 Chen Y, Guo J, Healy DP. Risk of hepatotoxicity associated with the use of telithromycin: A signal detection using data mining algorithms. Ann Pharmacother . 2008; 42: 1791-96

90 Chen Y; Guo J, Steinbuch M et al. Comparison of sensitivity and timing of early signal detection of four frequently used signal detection methods: An empirical study based on the US FDA adverse event reporting system database. Pharmaceut Med. 2008; 22(6): 359-365

91 Li C, Xia J, Deng J. A web-based quantitative signal detection system on adverse drug reaction in China. Eur J Clin Pharmacol. 2009; 65(7):729-41.

92 Poluzzi E, Raschi E, Moretti U et al. Drug-induced torsades de pointes: Data mining of the public version of the FDA Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf. 2009;18(6):512-8.

93 Ahmed I, Haramburu F, Fourrier-Réglat A et al. Bayesian pharmacovigilance signal detection methods revisited in a multiple comparison setting. Stat Med. 2009; 28(13):1774-92.

94 Hochberg AM, Hauben M, Pearson RK et al. Systematic investigation of time windows for adverse event data mining for recently approved drugs. J Clin Pharmacol. 2009; 49(6):626-33

95 Alvarez Y, Hidalgo A, Maignen F et al. Validation of statistical signal detection procedures in eudra vigilance post-authorization data: A retrospective evaluation of the potential for earlier signalling. Drug Saf. 2010; 33(6):475-87.

96 Chen J, Wei Y, Sun J. Research on signal detection methods based on data mining in adverse drug reaction of Shuanghuanglian injection. Zhongguo Zhong Yao Za Zhi. 2010; 35(3):308-12

97 Prescription –Event Monitoring by Saad A.W. Shakir. Pharmacoepidemiology, Fourth Edition. Edited by B.L. Strom. 2005 John Wiley & Sons Ltd.

98 Mann RD. Prescription-event monitoring-recent progress and future horizons. Br J Clin Pharmacol 1998; 6 195-201

99 Ferreira G. Prescription-Event Monitoring. Developments in Signal Detection. Drug Safety 2007; 30 (7): 639-641

100 Heeley E, Wilton LV and Shakir SAW. Automated Signal Generation in Prescription-Event Monitoring. Drug Saf 2002; 25(6) 423-432

101 Layton D, Marshall V, Boshier A et al. Serious Skin Reactions and Selective COX-2 Inhibitors A Case Series From Prescription-Event Monitoring in England. Drug Saf. 2006;29(8):687-96.

102 National Health Expenditure database, Drug expenditure in Canada, 1985 to 1998;[online]. Available from URL: http://secure.cihi.ca/cihiweb/products/drug_expenditure_1985_2008_e.pdf. [Accessed 25 Feb 2012]

103 Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005; 58(4):323-37

104 Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003; 12(1): 17–29

105 Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf 2004; 27(12): 871–881.

106 Nixdorff N, Hustey FM, Brady AK et al Potentially inappropriate medications and adverse drug effects in elders in the ED. Am J Emerg Med. 2008; 26: 697–700.

107 International Conference on Harmonisation. Studies in support of special populations: Geriatrics . ICH Harmonised Tripartite Guideline. Endorsed by the ICH Steering Committee at Step 4 of the ICH Process 24 June 1993. [online]. Available from URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Step4/E7_Guideline.pdf. [Accessed 2013 May 12

108 Monfared AA, Lelorier J. Accuracy and validity of using medical claims data to identify episodes of hospitalizations in patients with COPD. Pharmacoepidemiol Drug Saf. 2006;15(1):19-29

109 Wilchesky M, Tamblyn R, Huang A. Validation of diagnostic codes within medical services claims. J Clin Epidemiol 2004. 57:131–141

110 Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. Am J Epidemiol.158 (9); 915-920.

111 Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect on non-experimental pharmacoepidemiological research. J Clin Epidemiol. 1994 47 (7) 731-737.

112 Petri H, Urquhrat J. Channelling bias in the interpretation of drug effects. Stat Med. 1991;. 10 (4): 577-581

113 Schneeweiss S, Seeger JD, Maclure M, et al. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol. 2001 1;154(9):854-64.

114 Moride Y, Ducruet T, Boivin JF, et al. Prescription channeling of COX-2 inhibitors and traditional nonselective nonsteroidal anti-inflammatory drugs: a population-based case–control study. Arthritis Res Ther. 2005;7(2):R333-42.

115 von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol. 1992;45:197–203

116 Développement et validation d'un index de prédiction des risques d'institutionnalisation et de décès pour le contrôle des variables confondantes non-mesurées dans la population âgée. [dissertation]. Montreal (QC): Université de Montréal. [online] Also available from http://hdl.handle.net/1866/6245

117 Sikka R, XiaF, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care 2005 ; 11 : 449-457

118 Miettinen O. Estimability and estimation in case-referent studies. Am. J. Epidemiol. (1976) 103 (2): 226-235.

119 Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol Drug Saf 2010; 19(8): 858–868

120 Everitt, B.S. Cambridge Dictionary of Statistics. Second Edition. 2002. Cambridge University Press. New York (NY).

121 Rahme E, Watson DJ, Kong SX et al. Association between nonnaproxen NSAIDs, COX-2 inhibitors and hospitalization for acute myocardial infarction among the elderly: a retrospective cohort study. Pharmacoepidemiol Drug Saf. 2007 May;16(5):493-503.

122 Geographical variation of Crohn's disease residual incidence in the Province of Quebec, Canada. Int J Health Geogr. 2010 May 12;9:22.

123 Perreault S, Blais L, Lamarre D et al. Persistence and determinants of statin therapy among middle-aged patients for primary and secondary prevention. Br J Clin Pharmacol. 2005 May;59(5):564-73

124 Régie l'Assurance Maladie du Québec. Health Ministry, Government of Québec, Québec: Régie de l'Assurance Maladie du Québec; Québec 1997.

125 Birman-Deych E, Waterman AD, Yan Y et al. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care. 2005 May; 43(5): 480-5.

126 Motola D, Poluzzi E, Marra A, et al. Safety Profile of Thiazolidinediones on the Basis of the FDA-AERS Database : Cardiovascular and Bone Fracture Risks for Rosiglitazone and Pioglitazone. Abstracts of 26th ISPE . Pharmacoepidemiol Drug Saf, 2010; 19: S129

127 Schneeweiss S, Rassen JA, Glynn RJ et al. High-dimensional Propensity score Adjustment in Studies of Treatment Effects Using Health Care Claims Data. 2009. Epidemiology : 20 (4) 512-22.

128 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457-71.

129 Nissen SE, Wolski K. Rosiglitazone Revisited An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality.Arch Intern Med. 2010;170(14):1191-1201

130 Gerstein HC, Yusuf S, Bosch J, et al; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006;368(9541):1096-1105

131 A new strategy for detection of signals in the WHO database 2002. Uppsala Reports 2001 Nov; 17: 8-9

132 Trifiro` G, Pariente A, Coloma PM, et al., on behalf of the EU-ADR consortium. Data 420 mining on electronic health record databases for signal detection in pharmacovigilance: 421 which events to monitor? Pharmacoepidemiol Drug Saf 2009; 18 (12): 1176-84

133 Schulte PFJ. Risk of Clozapine-Associated Agranulocytosis and Mandatory White Blood Cell Monitoring. Ann Pharmacother 2006;40:683-8

134 Touw DJ, Neef C, Thomson, AH, et al. Cost Effectiveness of Therapeutic Drug Monitoring: an update. EJHP Science . 2007 4(13); 83-91

135 Brinker A, Kornegay C, Nourjah P. Trends in Adherence to a Revised Risk Management Program Designed to Decrease or Eliminate isotretinoin-exposed Pregnancies. Arch Dermatol. 2005;141:563-569.

136 Medicines and Health Care Products Regulatory Agency. Black Triangle Scheme. [online] Available from URL: http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Reportingsuspectedadversedrugreactions/Healthcareprofessionalreporting/BlackTriangleScheme/CON024119. [Accessed 2012 January 25]

137 Leiderman DB. Risk Management of Drug Products and the Food and Drug Administration: Evolution and context. Drug Alcohol Depend 2009 ; 105S : S9–S13

138 Medicines and Health Care Product Regulatory Agency. Patient Reporting to the Yellow Card System: evaluation. [online] Available at URL: http://www.mhra.gov.uk/NewsCentre/CON2023600. [Accessed 2012 January 25]

139 Health Canada. Draft Guidance Document for Industry - Triggers for Issuance of Risk Communication Documents for Marketed Health Products for Human Use.[online] Available from URL: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/triggers-elements_consultation-eng.pdf. [Accessed 2012 January 27]

140 Health Canada. Guidance for Industry - Issuance of Health Professional Communications and Public Communications by Market Authorization Holders [online] Available from URL: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/guid-dir_indust_hppc-cpsp-eng.pdf. [Accessed 2012 January 27].

141 Bihari, Michael. Black Box Warning: Box Denotes a Drug's Possible Serious Side Effects or Risks. [online] Available at URL: http://drugs.about.com/od/medicationabcs/a/BlackBoxWarning.htm. [Accessed 2011 Dec 17]

142 A health Canada Notice Regarding Implementation of Risk Management Planning including the adoption of ICH Guidance on Pharmacovigilance Planning- ICH Topic E2E.[online] Availablel at URL: www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/notice_avis_rmp_pgr-eng.php. [Accessed 2011 Dec 26]

The Food and Drug Administration Guidance for Industry. How to comply witht he Pediatric Research Equity Act. [online] available from URL: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf//www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf. [Accessed 2012 May 15]

144 Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. Br J Clin Pharmacol. 2004; 57(2):127-34.

145 Raymond CB, Morgan SG, Katz A et al. A Population Based Analysis of Statin Utilization in British Columbia. Clinical Therapeutics. 2007; 29(9): 2107-19

146 Clark JA, Klincewicz SL, Stang PE. Spontaneous adverse event signaling methods: classification and use with health care treatment products. Epidemiol Rev. 2001;23(2):191-210.

147 Hauben M, Norén GN.A decade of data mining and still counting. Drug Saf. 2010; 33(7):527-34.

148 Ray WA, Griffin MR, Schaffner W et al. Psychotropic drug use and the risk of hip fracture. N Eng J Med. 1987; 316:363-369

149 Levy M. Adverse reactions to over-the-counter analgesics: an epidemiological evaluation. Agents Actions Suppl. 1988;25:21-31

150 Sharrar RG. Interpreting the Guidelines on Risk Management Plans. Drug Safety. September/October 2008. [online] Available from URL: http://www.unitedbiosource.net/pdfs/in-the-news/interpreting-risk-management-plans.pdf. [Accessed 2012 May 18

151 Callreus T. Sentinel systems are needed for long term adverse drug reactions. BMJ 2005;330:255-256

152 Hallas J. Conducting pharmacoepidemiologic research in Denmark. Pharmacoepidemiol Drug Saf 2001;10:619–23.

153 EudraVigilance: pharmacovigilance in the European economic area [online]. Available from URL: http://eudravigilance.ema.europa.eu/lowres.htm [Accessed 2012 Jan 11]

Appendix I – Summary of Data Mining Study Variables

STUDY DRUG - code denomination commune	REFERENCE DRUG - code denomination commune	OUTCOME / EVENT - ICD-9 code	DRUG-AE PAIR TYPE	COVARIABLES
Rosuvastatin 46860	Other statins 47232; 47609; 47083; 47604; 45500; 45570; 47595; 45564	Rhabdomyolysis 728.8	Known association (positive)	N/A
Rosiglitazone 47371, 47652, 46642	Metformin 05824; 47208; 47807	Acute myocardial infarction	Known association (positive)	- Age in 5 categories: i) 66-69; ii) 70-74, iii)75-79, iv) 80-84, v) 85+) - Gender (dichotomous) - Chronic Disease Score in four categories: i) 0; ii) > 0- 5; iii) > 5 - 10, iv) >10
Pioglitazone 46678	Metformin 05824; 47208; 47807	Increased fractures 800 to 829, 733.1	Known association (positive)	- Age in 5 categories i) 66-69; ii) 70-74, iii)75-79, iv) 80-84, v) 85+) - Chronic Disease Score in four categories: i) 0; ii) > 0- 5; iii) > 5 - 10, iv) >10
Rosiglitazone 47371, 47652, 46642	Metformin 05824; 47208; 47807	Increased fractures 800 to 829, 733.1	Known association (positive)	- Age in 5 categories i) 66-69; ii) 70-74, iii)75-79, iv) 80-84, v) 85+) - Chronic Disease Score in four categories: i) 0; ii) > 0- 5; iii) > 5 - 10, iv) >10

Amitriptyline 00429 ; 00442 ; 46011	Metoprolol 38275; 46763; 46780	Increased fractures 800 to 829, 733.1	Negative-Control	- Age in 5 categories i) 66-69; ii) 70-74, iii)75-79, iv) 80-84, v) 85+) - Gender (dichotomous) - Chronic Disease Score in four categories: i) 0; ii) > 0- 5; iii) > 5 - 10, iv) >10
Alendronate 46295; 47165; 47662; 47747	Atenolol 43670; 46325	Acute hepatitis 573.3 & 570.x	Negative-Control	- Age in 5 categories i) 66-69; ii) 70-74, iii)75-79, iv) 80-84, v) 85+) - Gender (dichotomous) - Chronic Disease Score in four categories: i) 0; ii) > 0- 5; iii) > 5 - 10, iv) >10