Novel use of electronic health record (EHR) to estimate the prevalence of off-label prescribing, determinants and its association with adverse drug events (ADE)

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Thesis quote:

"We need to bring a bit of the Enlightenment to medicine. It is time to enter an "age of reason" when it comes to **starting** and **stopping** drugs."

Gordon D. Schiff, MD
(2002)

Abstract

Background

Adverse drug events (ADE) are costly and a leading cause of death. Physicians regularly prescribe drugs for indications for which they were never tested (off-label use), a factor that has been associated with some highly publicized ADEs. Current pharmacosurveillance methods are plagued by high rates of under reporting of ADE, and are too slow to adequately monitor drug safety and effectiveness. These methods also lack important clinical variables such as indication for treatment, laboratory indices and health outcomes that provide essential context for making rigorous safety and effectiveness decisions. In particular, the lack of information on treatment indication means that drugs are not evaluated in terms of their risks and benefits for a specific disease entity, but instead for all disease conditions where the drug may be prescribed. Because drug regulatory bodies and pharmaceutical companies cannot identify drug safety concerns in a timely fashion, or monitor off-label use, we urgently need to develop new methods of pharmacosurveillance. Electronic health records (EHR) may help fill this void if the reasons for a drug prescription (treatment indication) and the reason for drug discontinuation (e.g. adverse drug event, ineffectiveness) can be documented.

Objectives

1) To determine the accuracy of an electronic health record system in documenting orders for drug discontinuation and dose changes of prescription drug treatments, and to identify the reasons for drug discontinuation and dose change of medications.

2) To determine the sensitivity and positive predictive value of using an EHR to document treatment indications at the time of prescribing and investigate the use of treatment indication data to evaluate on- and off-label prescribing.

3) To evaluate the prevalence of off-label prescribing and drug, patient and physician determinants of off-label prescribing in primary care settings.

4) To determine the association between off-label use and adverse drug events, adjusting for important ADE determinants.

Methods

To fulfill these research objectives, I conducted four studies using the Medical office of the XXI century (MOXXI) EHR system, which was developed by McGill clinical and health informatics research group, to study the effect of implementing an EHR in primary care physician offices. First, I conducted a validation study to assess the sensitivity, specificity, positive and negative predictive value of the MOXXI EHR system in documenting prescription drug discontinuation and dose-change orders by comparing information obtained from the MOXXI system with information from physician-facilitated chart review. Second, I conducted a validation study to assess the sensitivity and the positive predictive value of MOXXI EHR in documenting treatment indications at the time of drug prescribing and assess the use of treatment indication data to evaluate on- and off-label prescribing. Third, I estimated the prevalence of off-label prescribing in primary care and assessed the strength of scientific evidence for off-label prescribing. Moreover, the drug, patient and physician determinants of off-label prescribing were assessed using alternating logistic regression model. Fourth, I assessed the association between off-label use and ADE using incident drug prescriptions, treatment indications and ADE data collected using an EHR (measures that were validated in study one and two). I fit a marginal Cox regression model to the data to account for the hierarchical structure of drugs within patients.

Results

Manuscript 1: The sensitivity of the EHR in identifying physician-initiated drug discontinuations and dose-changes was 67.0% (95% CI: 54.1, 77.7), the specificity was 99.7% (95% CI: 99.5, 99.9), the positive predictive value (PPV) was 97.3% (95% CI: 95.6, 98.7), after adjustment for verification biased sampling. The concordance between the reasons for drug discontinuation and dose change documented by the MOXXI application and the actual reasons reported in physician-facilitated chart review was 95.2% for ineffective treatment and 85.7% for adverse drug events.

Manuscript 2: The sensitivity of the EHR treatment indication was 98.5% (95% CI; 96.5%, 99.5%) and the PPV of the system in accurately identifying the treatment indication was 97.0% (95% CI; 94.2%, 98.6%). In addition, the treatment indication data collected using the EHR system allowed assessment of on- and off-label prescribing.

Manuscript 3: The prevalence of off-label use was 11.0% of 253,347 prescriptions written to 50,823 patients. An estimated 79.0% of off-label prescriptions lacked strong scientific evidence. Off-label use was highest for central nervous system drugs (26.3%), including anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%). The lowest off-label prescribing was for formulary-restricted drugs (2.9%) and blood and coagulation drugs (1.7%). Drugs with three or four approved indications were associated with less off-label use compared with drugs with one or two approved indications (6.7% vs. 15.7%; adjusted odds ratio [AOR], 0.44; 95% CI, 0.41-0.48). Drugs approved after 1995 were prescribed off-label less often than drugs approved before 1981 (8.0% vs. 17.0%; AOR, 0.46; 95% CI, 0.42-0.50). Patients with a Charlson Comorbidity Index of one or higher had lower off-label use than did patients with an index of 0 (9.6% vs. 11.7%; AOR, 0.94; 95% CI, 0.91-0.97). Physicians with evidence-based orientation were less likely to prescribe off-label (AOR, 0.93; 95% CI, 0.88-0.99), a 7% reduction per 5-points in the evidence subscale of the Evidence-Practicality-Conformity Instrument.

Manuscript 4: The off-label ADE rate (19.8/10,000 person-months) was higher than on-label uses (12.5 per 10,000 person-months) [HR, 1.43 (95% CI, 1.29, 1.59)]. Off-label uses which lacked scientific evidence had an even higher ADE rate (21.8 per 10,000 person-months compared to on-label uses [HR, 1.53 (95% CI, 1.37, 1.72)]. Other factors associated with an increased risk of ADEs included: patients who had received eight or more drugs had increased risk of ADE than patients with one or two drugs [HR, 5.77 (95% CI, 4.77, 6.97)]; anti-infective drugs compared to gastrointestinal drugs [HR, 6.08 (4.39, 8.43)], patients in the bottom quartile for age (18 – 47.5 years) had higher risk of ADE compared to the three older quartiles. Females had higher risk of ADE than males [HR, 1.12 (95% CI, 1.02, 1.24)]. Drugs approved after 1981 had greater risk of ADE than drugs approved before 1981. A one-unit increase in continuity of care index increased the ADE detection by 20% [HR, 1.20, (95% CI, 1.13, 1.27).

Conclusion

In this thesis, I have shown for the first time that an EHR system can accurately document physician-identified treatment indications and adverse drug events and other treatment

outcomes, and that this documentation can be easily integrated into the clinical work flow. The treatment indication data could be used to measure prevalence of off-label use and identify important determinants of off-label use which included drug, patient and physician characteristics. In addition, the treatment indication data could be combined with drug treatment outcome data to create a novel pharmacosurveillance tool. Moreover, it was demonstrated that off-label prescribing is an independent determinant of adverse drug events. Future EHRs should be designed to enable post-market surveillance of drugs by incorporating treatment indications and treatment outcomes to monitor the safety and effectiveness of on- and off-label uses of drugs.

Résumé

Contexte

Les effets indésirables des médicaments (EIM) sont coûteux et l'une des principales causes de mortalité. Les médecins prescrivent souvent des médicaments pour des indications pour lesquelles ils n'ont jamais été approuvés (c.-à-d., usage non indiqué), un facteur qui a été associé à certains EIM hautement médiatisés. Les méthodes actuelles de pharmacovigilance sous-estiment l'incidence des EIM, et sont souvent trop lentes afin de surveiller adéquatement la sécurité et l'efficacité des médicaments. Ces méthodes ne tiennent également pas compte de variables cliniques importantes, dont l'indication de traitement, les résultats de laboratoire et les résultats de santé, lesquelles fournissent des éléments de contexte essentiels afin d'évaluer la sécurité et l'efficacité des médicaments. En particulier, le manque d'information à l'égard de l'indication de traitement signifie que les médicaments ne sont pas évalués en fonction de leurs risques et de leurs bénéfices pour une condition de santé en particulier, mais plutôt pour toutes les maladies pour lesquelles ils peuvent être prescrits. En conséquence, les organismes de réglementation des médicaments et les compagnies pharmaceutiques ne peuvent pas identifier les dangers potentiels des médicaments en temps opportun, ou encore surveiller l'usage non indiqué de ces derniers. Pour ces raisons, de nouvelles méthodes de pharmacovigilance doivent être développées. À cette fin, les dossiers de santé électroniques (DSE) pourraient être utiles, notamment si l'indication de traitement et la raison justifiant l'arrêt d'un médicament (p.ex. : un effet indésirable, inefficacité) y sont documentées.

Objectifs

1) Déterminer l'exactitude d'un DSE à documenter les ordonnances d'arrêt de traitement médicamenteux et de changement de doses, ainsi que pour identifier les raisons de l'arrêt du traitement médicamenteux et du changement de dose;
2) Déterminer la sensibilité et la valeur prédictive positive d'un DSE à documenter les indications de traitement au moment de la prescription, et investiguer l'utilisation de l'indication de traitement afin d'évaluer l'usage indiquée et non indiquée des médicaments d'ordonnance;

3) Évaluer la prévalence des prescriptions non indiquées et les caractéristiques des médicaments, des patients et des médecins étant associées à un usage non indiqué des médicaments en soins primaires.
4) Déterminer l'association entre l'utilisation non indiquée des médicaments et les EIM, après avoir ajusté pour les déterminants importants des EIM.

Méthodes

Pour atteindre ces objectifs de recherche, j'ai réalisé quatre études en utilisant le *Medical Office of the XXI century* (MOXXI). MOXXI est un DSE qui a été développé par le Groupe de recherche en informatique clinique et de la santé de l'Université McGill afin d'étudier les effets de la mise en place d'un DSE dans les cabinets de médecins œuvrant en soins primaires. Premièrement, j'ai mené une étude de validation afin d'évaluer la sensibilité, la spécificité et les valeurs prédictives positive (VPP) et négative (VPN) du DSE MOXXI à documenter les ordonnance d'arrêt des médicaments ou de changement de dose, et ce en comparant les informations obtenues dans MOXXI à celles obtenues auprès du médecin traitant après consultation du dossier médical. Deuxièmement, j'ai mené une étude de validation afin d'évaluer, d'une part, la sensibilité et la VPP de MOXXI à documenter les indications de traitement au moment de la prescription de médicaments et, d'autre part, afin d'évaluer l'utilisation des données au sujet de l'indication de traitement afin de juger de l'usage indiquée ou non des médicaments. Troisièmement, j'ai estimé la prévalence de l'usage non indiqué des médicaments en soins primaires ainsi qu'évalué la robustesse des preuves scientifiques supportant ce type d'usage. De plus, les caractéristiques des médicaments, des patients et des médecins associés à un usage non indiqué des médicaments ont été évaluées par le biais de modèles de régression logistique alternatifs. Quatrièmement, j'ai évalué l'association entre l'usage non indiqué des médicaments et les EIM en utilisant des prescriptions incidentes de médicaments, les indications de traitement et les données recueillies sur les EIM dans MOXXI (des mesures validées lors de l'étude un et deux). Pour ce faire, j'ai ajusté un modèle marginal de régression Cox aux données, et ce afin de tenir compte du fait que les médicaments sont nichés dans les patients.

Résultats

Manuscrit 1: La sensibilité de MOXXI à identifier des arrêts de traitements ou des changements de doses initiés par le médecin est de 67,0% (IC à 95%: 54,1 - 77,7), la spécificité est de 99,7% (IC 95%: 99,5, 99,9), la VPP est de 97,3% (IC à 95%: 95,6 - 98,7), et ce après avoir ajusté pour le biais d'échantillonnage de vérification. La concordance entre les raisons pour arrêter un médicament ou pour en changer la dose, telles que documentées dans MOXXI, et les raisons réelles, telles que déclarées par le médecin traitant après vérification du dossier médical, était de 95,2% pour les traitements inefficaces et de 85,7% pour les EIM.

Manuscrit 2: La sensibilité de l'indication de traitement documentée dans MOXXI était de 98,5% (IC à 95%; 96,5% - 99,5%) et la VPP de ce DSE à identifier avec précision les indications de traitement était de 97,0% (IC à 95%, 94,2% - 98,6%). De plus, les données relatives aux indications de traitements recueillies au moyen de MOXXI ont permis d'évaluer l'usage indiqué ou non des médicaments d'ordonnance.

Manuscrit 3: La prévalence de l'usage non indiqué des médicaments est de 11,0% parmi 253 347 prescriptions reçues par 50 823 patients. On estime que 79,0% des prescriptions non indiquées ne sont pas justifiées empiriquement. L'usage non indiqué des médicaments est le plus élevé pour les médicaments du système nerveux central (26,3%), y compris les anticonvulsivants (66,6%), les antipsychotiques (43,8%) et les antidépresseurs (33,4%). Le plus bas taux d'usage non indiqué est pour les médicaments à usages restreints (2,9%) et ceux pour le sang et la coagulation (1,7%). Les médicaments avec trois ou quatre indications approuvées sont associés à un taux moindre d'usage non indiqué par rapport aux médicaments n'ayant qu'une ou deux indications approuvées (6,7% vs 15,7%; rapport de cotes ajusté [RCA] : 0,44; IC à 95% : 0,41 - 0,48). Les médicaments approuvés après 1995 sont prescrits de manière non indiquée moins souvent que les médicaments approuvés avant 1981 (8,0% vs 17,0%; RCA : 0,46; IC 95% : 0,42 à 0,50). Les patients ayant un indice de comorbidité de Charlson de 1 ou plus ont un risque plus faible d'être exposés à un usage non indiqué des médicaments que les patients présentant un indice de 0 (9,6% vs 11,7%; RCA : 0,94; IC 95% : 0.91 - 0.97). Les médecins dont le processus de prise de décision est davantage fondé sur les preuves sont moins susceptibles de prescrire pour des usages non

indiqués (RCA : 0,93; IC 95% : 0.88 - 0,99), soit une réduction de 7% pour chaque 5 points additionnels sur la sous-échelle *Evidence* de l'instrument *Evidence-Practicality-Conformity*.

Manuscrit 4:

Le taux d'EIM associé à un usage non indiqué des médicaments (19.8/10 000 personnes-mois) est plus élevé que celui pour les usages indiqués (12,5 pour 10.000 personnes-mois) [HR : 1,43; IC à 95% : 1,29 - 1,59)]. Les usages non indiqués, non justifiés empiriquement, ont un taux encore plus élevé d'EIM (21,8 pour 10.000 personnes-mois) par rapport aux usages indiqués [HR : 1,53; IC à 95% : 1,37 - 1,72]). Les autres facteurs associés à un risque accru d'EIM incluent: a) les patients ayant reçu huit médicaments ou plus par rapport aux patients n'ayant reçu qu'un ou deux médicaments [HR : 5,77; IC à 95% : 4,77 - 6,97]; b) les médicaments anti-infectieux par rapport aux médicaments gastro-intestinaux [HR : 6,08; 4,39 - 8,43]; c) les patients dans le quartile inférieur de l'âge par rapport aux patients des trois quartiles supérieurs; d) les femmes par rapport aux hommes [RH : 1,12; IC à 95% : 1,02 - 1,24)]; d) les médicaments approuvés après 1981 par rapport aux médicaments approuvés avant 1981. La continuité des soins augmente la détection des EIM [HR : 1,20; IC à 95% : 1,13 - 1,27), et ce pour chaque unité additionnelle de continuité des soins.

Conclusion

Dans cette thèse, j'ai montré pour la première fois qu'un DSE peut documenter avec précision les indications de traitement telles qu'identifiées par un médecin, les événements indésirables et les autres résultats du traitement médicamenteux, et que cette documentation peut être facilement intégrée dans le flux de travail clinique. Les données d'indication de traitement pourraient être utilisées pour mesurer la prévalence de l'usage non indiqué des médicaments et pour identifier des déterminants importants de ce type d'usage, dont les caractéristiques des médicaments, des patients et des médecins. En outre, les indications de traitement pourraient être combinées aux résultats des traitements médicamenteux, et ce afin de créer un nouvel outil de pharmacovigilance. De plus, il a été démontré que l'usage non indiqué des médicaments est un déterminant indépendant des EIM. Dans le future, les DSE devraient permettre la surveillance post-commercialisation des médicaments; notamment en intégrant les indications et les résultats de traitement, et ce afin d'assurer la sécurité et l'efficacité de l'usage indiquée et non des médicaments.

Statement of originality

Adverse drug events (ADE) are a leading cause of death. Current pharmacosurveillance methods are slow and inadequate in addressing critical questions of drug safety and effectiveness. These methods are plagued by high rates of under-reporting of ADE. Moreover, off-label use, which has received little attention until recently, has been identified as an important contributor to preventable ADE. Despite concerns for adverse outcomes, there has been no systematic investigation of the effects of off-label use in adult populations in real world situation. The paucity of knowledge is in part related to the methodological challenges of measuring off-label use and its effects; specifically the lack of link between prescribed drugs and their indication for use and follow-up of these drug uses to determine treatment outcomes. Moreover, drug regulatory bodies are moving towards a life-cycle approach of drug evaluation, with greater emphasis on ongoing pharmacovigilance than traditional pre-marketing approval. The work in this thesis addresses these multifaceted problems of prescription drug surveillance and represents an original and important contribution to the methodology of pharmacosurveillance and the monitoring of off-label uses using electronic health records.

The research included in this thesis is the first to:

1. evaluate the accuracy of drug discontinuation and dose-change orders documented in an electronic health record system to determine if this information could be used to identify physician-identified adverse drug events and other drug treatment outcomes.
2. evaluate the accuracy of treatment indications documented in an electronic health record system to determine if this information could be used to evaluate on-label and off-label prescribing.
3. use treatment indication data documented at the time of drug prescribing to determine the prevalence of off-label prescribing and the prevalence of off-label prescribing without strong scientific evidence.
4. evaluate determinants of off-label prescribing, incorporating drug, patient and physician characteristics at the same time by using alternating logistic regression.
5. identify treatment indications for which Health Canada has not approved any drugs for use in a primary care setting.

6. investigate the association between off-label prescribing and adverse drug events in a cohort study in an adult population in a primary care setting.
7. validate treatment indication data using physician-facilitated chart review with the prescribing physician's direct input, in contrast to chart review without physician input.

This research makes an important contribution to pharmacosurveillance and patient safety. Specifically, the research contributed to a priority area identified by the World Health Organization to incorporate active surveillance to drug monitoring activities. I showed that electronic health records can document treatment indications at the time of prescribing and may allow active and enhanced post-marketing evaluation of drugs if linked to treatment outcomes. In addition, off-label prescribing can be monitored using electronic health records. Finally, off-label use was associated with adverse drug events in an adult population. These findings have important implications for patients, physicians, pharmaceutical companies, drug regulatory bodies and researchers. The work reported in this thesis was identified as one of the 'Emerging Sources of Information on the Safety of Off-Label Use of Medicines' by the director of Office of Surveillance and Epidemiology of the FDA.

With active guidance and feedback from my thesis supervisor and committee members, I generated the research hypotheses, reviewed the literature, developed the study protocols and methods, performed all data management and statistical analyses, interpreted the findings and wrote all four manuscripts. I developed the questionnaire for the physician-facilitated chart review and I was also involved with data collection. Moreover, I operationalized and created the different predictors of off-label prescribing and adverse drug events.

The dissertation comprises a review of the literature on pharmacosurveillance and new initiatives in the field, off-label prescribing and adverse drug events, two manuscripts reporting on the validation of drug treatment changes and treatment indications, and two manuscripts on the prevalence and determinants of off-label prescribing and the association between off-label use and adverse drug events.

Contribution of authors

Manuscript 1: Eguale T, Tamblyn R, Winslade NE, Buckeridge DL. Detection of adverse drug events and other treatment outcomes using an electronic prescribing system. *Drug Safety*. 2008;31(11):1005-16.

Manuscript 2: Eguale T, Winslade NE, Hanley JA, Buckeridge DL ,Tamblyn R. Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic-prescribing: A validation study in Canada. *Drug Safety*. 2010;33(7):559-67

Manuscript 3: Eguale T, Buckeridge DL, Winslade NE, Benedetti A, Hanley JA, Tamblyn R. Drug, patient and physician determinants of off-label prescribing in primary care setting. *Arch Intern Med*. 2012;172(10):781-788.

Manuscript 4: Eguale T, Buckeridge DL, Winslade NE, Benedetti A, Hanley JA, Tamblyn R. Off-label use is a determinant of adverse drug events. (prepared for submission)

All the manuscripts were co-authored and I am the lead author in all four manuscripts. Moreover, I generated the research hypotheses, reviewed the literature, developed the study protocols and methods, performed all data management and statistical analyses, interpreted the findings and wrote all four manuscripts, with the guidance of my supervisor and thesis committee members.

Robyn Tamblyn is a James McGill Chair, and a Professor in the Department of Medicine and the Department of Epidemiology, Biostatistics and Occupational Health at McGill University. She is the founder and scientific director of the Clinical and Health Informatics Research Group at McGill University. She is also the Scientific Director of the Institute of Health Services and Policy Research (IHSPR) at the Canadian Institutes of Health Research (CIHR), Scientist at the McGill University Health Centre Research Institute and fellow of the Canadian Academy of Health Sciences. As my thesis supervisor, she oversaw all aspects of the thesis development and execution including the development of the research methods, statistical analyses and interpretation of results, and provided editorial feedback on all four manuscripts and the thesis.

David Buckeridge holds a Canada Research Chair in Public Health Informatics, and is an Associate Professor in the Department of Epidemiology, Biostatistics and Occupational

Health at McGill University. He is also a medical consultant to the Montreal Public Health Department and the Quebec National Public Health Institute. As a thesis committee member, he provided input in all aspects of thesis development and execution and was actively involved in the interpretation of the results and provided editorial feedback on all four manuscripts.

Nancy Winslade, BScPhm., PharmD., MHPE, is an Assistant Professor in the Department of Medicine, Division of Geriatrics at McGill University, working with the Medical Office of the 21st Century Research Project. As a co-author and a pharmacist, she provided input in the development of the research protocol, interpretation of results and also edited all four manuscripts and suggested revisions.

James A. Hanley is a Professor, Department of Epidemiology, Biostatistics and occupational health, Associate Member Department of Mathematics and Statistics of McGill University and senior scientist at the Division of Clinical Epidemiology in Royal Victoria Hospital. He was actively involved in the protocol development of all the studies and oversaw the statistical analyses and interpretation of results of all four manuscripts.

Andrea Benedetti is an associate professor in the Department of Epidemiology, Biostatistics and occupational health of McGill University and Respiratory Epidemiology & Clinical Research Unit, Montreal Chest Institute. As a thesis committee member, she was actively involved with developing the methodologies for the statistical analyses in the third and fourth manuscripts involving correlated data; her area of expertise.

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This thesis is dedicated to my wife, Senait Kagnew, and my daughters - Fikir and Eden, whose love and support get me to this day.

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Chapter 1: Introduction

Context

Prescription drugs play an ever-expanding and important role in the prevention and treatment of common health problems. Over 60% of adult Canadians have used at least one prescription drug in the past 6 months, and six or more drugs are taken by 18% of the elderly(1). At the same time, direct expenditure associated with prescription drugs has escalated rapidly since 1996 and has recently surpassed costs associated with physician services in Canada(2). Moreover, indirect costs due to adverse drug events (ADEs) are considerable. More than one-third of Canadians reported having an adverse drug event due to prescription drugs in a six-month period and two-thirds of patients consult their physicians when they suspect an ADE (1). In the USA, ADEs cost more than 30 billion dollars annually (3) and are a leading causes of mortality (4) but responding to ADEs through drug withdrawal is often a long and protracted process (5). A major contributing factor to ADEs that has received little attention until recently, is the regular practice of physicians to prescribe or administer drugs outside the context of formal testing. The inability of the current system, including the drug regulatory bodies and the pharmaceutical companies, to monitor drugs in general and off-label used drugs in particular, after their approval to identify safety concerns in a timely fashion points to an urgent need to develop new methods of pharmacosurveillance and strengthen the current ones.

Evaluating the safety and effectiveness of drug therapy following drug approval

Most countries have established a formal regulatory process for drug approval that defines the information required from the drug manufacturers to demonstrate a drug's safety and efficacy. However, drugs are typically tested in randomized controlled trials with a limited number of patients that are carefully selected to optimize compliance and limit comorbidity (6-8). These study groups are rarely representative of the majority of patients treated with the drug after approval. While pre-market studies uncover commonly occurring ADEs, they are not designed to detect rare but serious ADEs (9). Experience from drugs withdrawn from the market in the 1990s due to serious ADEs reveals that the number of people exposed to a

drug at the pre-marketing stage is in the range of 340 to 5000 worldwide, while the number of patients treated with the same drugs prior to the withdrawal for the U.S. market alone ranged from 0.6 to 7.5 million (7).

Current pharmacosurveillance methods are slow and inadequate in addressing critical questions of drug safety and effectiveness (6;10). Spontaneous reporting of ADE are plagued by high rates of under-reporting of adverse drug events (10-12), including fatal ADEs (13). Spontaneous reporting also lacks denominators (number of patients exposed to a drug) to estimate incidences (6;10). While Prescription event monitoring (PEM) has a better response rate from physicians than spontaneous reporting of ADE in uncovering common ADEs, the response rate decreased tremendously when repeated requests were made to reporting physicians (14;15). Moreover, both spontaneous reporting and PEM methods are not aligned to the day-to-day activities of physicians, especially primary care physicians, who are responsible for the majority of prescriptions written (16). Pharmacoepidemiological studies based on administrative heath data or computerized health records are credited for the discovery of several safety issues of drugs, however together with the other reporting systems, they lack important clinical variables such as indication for treatment, risk factors (e.g. smoking, alcohol consumption), physical examination and laboratory indices (e.g. blood pressure, weight, glycosylated hemoglobin [HbA1c]) and health outcomes (quality of life, functional status) that provide essential context for making rigorous safety and effectiveness decisions.

Adequate evaluation of medication safety and effectiveness is further complicated when drugs are prescribed on an off-label basis. Off-label use is defined as the use of a prescription drug for an indication, in a dosage form, dose regimen, or for a particular population not covered by the approved labeling where safety and efficacy were assessed (17). Two landmark studies found that off-label prescribing by office-based physicians is common, occurring in 21% to 31% of all written prescriptions (18;19). However, off-label prescribing is more prevalent in specific subpopulations of patients. For example, over 80% of all drugs prescribed for children are off-label, due largely to limited drug testing conducted in children (20). Off-label prescribing is also common among cardiac medications, anticonvulsants and anti-asthma drugs ranging from 42 to 46% and therapies for psychiatric illness and allergies

are reported to have the highest rate of scientifically unsupported off-label use—96% and 89%, respectively (18). Some of the off-label uses are extensions of the approved indications and might be justified depending on the availability of alternative drugs and patients' comorbid conditions. However, these drugs were not rigorously tested for the off-label indications and their safety and effectiveness profile in relation to the off-label indication is generally unknown.

As a result, off-label prescribing is potentially dangerous. Few studies in children demonstrated the increased risk of ADEs in off-label use of drugs (21-25). In contrast, there is little systematic investigation in adult populations of the risk of off-label use since off-label use in adults is typically defined by treatment indication—indications for which the drug was not approved - and there is a methodological challenge of measuring off-label use and its effects; specifically the lack of link between prescribed drugs and their indication for use (26;27).The lack of systematic documentation of treatment indications in practice has severely curtailed comprehensive investigation of the prevalence and outcomes of off-label use (26). Investigation of off-label prescribing in adults is mainly based on physician surveys and administrative health data which are prone to misclassification bias and they also do not have follow-up data on patient outcomes which can inform the occurrence of ADEs. Despite notable cases and the continuous occurrence of severe ADEs in off-label drug treatment situations (e.g. fen-phen, quinine, tiagabine and hormonal replacement therapy (28-31)), there is no concerted effort by drug regulatory bodies or the pharmaceutical industry to actively investigate the risk of off-label uses other than the coordination of voluntary reporting of adverse drug events. However, there is worldwide consensus that post-marketing surveillance of the safety and effectiveness of drugs is crucial to quantify previously recognized as well as unexpected ADEs, and to evaluate the safety and effectiveness of on-label and off-label drug use in real world situations (26;32;33).

Computerization of medical care and electronic health record may address the two issues discussed previously: the inadequacies of present-day pharmacosurveillance methods in capturing adverse drug events in a timely and more comprehensive manner and the lack of treatment indication to monitor off-label prescribing and use.

Canadian context, electronic health record and the future in pharmacosurveillance

Canada, through its investment in the inter-operable electronic health record by Canada Health Infoway, has led the way in developing the next generation of electronic health record systems to overcome some of the limitations in pharmacosurveillance methodologies (34). Through the development and enforcement of national information standards, software is being developed to improve the structuring and coding of information at the time it is entered. Universal identifiers have been developed to track patients from one practice or province to another, ascertain previous health episodes or identify first-ever prescription of a drug. Most importantly, most provinces are establishing regional and provincial repositories that will allow complete clinical histories of laboratory, imaging and prescription data to be assembled for each member of the population. These developments will ultimately provide some of the essential clinical data to enhance administrative databases.

Following trends in Europe, Australia and the United States, Canada is following suit by prioritizing the implementation of electronic prescribing in ambulatory care (34), to reduce avoidable errors in prescribing and dispensing (35-37). The US center for Medicare and Medicaid services has identified that this is a sufficiently critical safety issue to adopt a uniform requirement for electronic prescribing for all physicians billing for patients enrolled in the Medicare Prescription Drug Program (38). This multi-national trend to adopt electronic prescribing opens new avenues for enhancing the information available for surveillance of drug safety and effectiveness. In particular, it provides an opportunity to incorporate information about indication for treatment as well as physician judgment, at the time of adverse event detection, information that is a critical benefit in traditional adverse event reporting systems. Specifically, both electronic documentation of treatment indication and transmission of orders to discontinue or change the dose of medication are considered to be among the critical features that should be incorporated into electronic prescribing and electronic health record systems to improve drug safety (37;39;40). Treatment indication documentation would allow off-label use to be monitored as well as to generate diagnosis-based reminders for drug selection and follow-up. Drug discontinuation orders may be an important signal of an adverse event, that can be captured in real-time from electronic prescribing systems, particularly if the reason for treatment change is also documented, as

most adverse drug events identified by physicians lead to a discontinuation or change in medication (39;41-45). In principle, all physician-initiated treatment changes can be documented. Treatment indications and reasons for stopping or changing medications, such as adverse drug reaction or ineffective treatment could be required as a mandatory field at the time of drug discontinuation, as has been done by the Partners group in Boston (46) and the MOXXI group in Quebec (47). Reports could be collected automatically and analyzed systematically to calculate the rate of off-label use, incidence of adverse drug events and ineffective treatments, and to compare the rates of adverse events among different drugs in real-world patient populations according to the treatment indication. The development and standardization of these methods both nationally and internationally could enhance the amount and quality of data available for conducting accurate and timely evaluation of the safety and effectiveness of drugs.

As utilization of electronic prescribing systems to document treatment indications and changes in therapy has yet to be validated, a set of studies was first undertaken to investigate the validity of using this approach to identify ADEs and treatment indications and assess the frequency of off-label use in an integrated community-based electronic health record system. The determinants and consequences of off-label use was then assessed to evaluate its importance from and clinical and population health perspective.

Research Objectives

The purposes of my thesis were to evaluate the accuracy of electronic health record to document prescription orders for drug treatment change and treatment indication, to determine the prevalence and determinants of off-label prescribing and to evaluate whether off-label use was a determinant of adverse drug events. The specific objectives were:

1) To determine the accuracy of an electronic health record system in documenting orders for drug discontinuation and dose changes of prescription drug treatment; and identifying the reasons for the drug discontinuation and dose change of medications.
2) To determine the sensitivity and positive predictive value of using an electronic prescribing system to document treatment indications at the time of prescribing; and investigate the use of treatment indication data to evaluate on- and off-label prescribing in primary-care practice.
3) To evaluate the prevalence of off-label prescribing and drug, patient and physician determinants of off-label prescribing in primary care setting
4) To determine the association between off-label use and adverse drug events

Organization of the thesis

This thesis is organized around four research manuscripts and the next chapter provides the background for these manuscripts. The first part of the background deals with the current state of pharmacosurveillance and its limitations, new initiatives, and the increasing role of electronic health record. The second part of the background dealt with the topic of off-label prescribing, how it is studied currently and the limitation of current methods, and the various determinants of off-label prescribing. The third chapter deals with the methodology of the thesis including data sources for the studies, data collection methods, and the various statistical methods. The next four chapters (chapters 4 – 7) include the manuscripts pertaining to the above four thesis objectives. Chapter 4 discusses the feasibility using EHR to document treatment discontinuations and dose change orders at the point-of-care in primary care setting, and a manuscript entitled "Detection of adverse drug events and other treatment outcomes using an electronic prescribing system" was published in *Drug Safety*.

Chapter 5 discusses the accuracy of EHR in documenting treatment indication and the feasibility of using the data to measure off-label prescribing, and a manuscript entitled "Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic-prescribing: a validation study in Canada" was published in *Drug Safety*. Chapter 6 deals with the prevalence of off-label prescribing and the various determinants, and a manuscript entitled "Drug, patient and physician determinants of off-label prescribing in primary care setting" was published in the *Archives of Internal Medicine*. Chapter 7 deals with the association between off-label use and adverse drug events and a manuscript entitled "Off-label use is a determinant of adverse drug events" is prepared for publication. Chapter 8 discusses the main findings of the thesis, their strength and limitations, their implications at various levels, and future research directions in pharmacosurveillance and monitoring of off-label prescribing.

Chapter 2: Background

Challenges in the Post-Market Surveillance of Prescription Drugs

Spontaneous reporting of adverse drug events

Following the thalidomide disaster, where drugs prescribed for nausea during pregnancy produced severe congenital anomalies, a voluntary system for spontaneous reporting of adverse drug events was instituted and continues to be the cornerstone of post-market surveillance (6). A total of 2.3 million adverse drug events were recorded in the US Adverse Drug Event Surveillance System from its inception in 1969 until 2002. The most frequent reason for ADE reports was ineffective treatment, (7%), followed by dermatitis (5.3%), headache (3.3%), pyrexia (1.8%), and dyspnea (1.5%) (48). The spontaneous reporting method has been successful in identifying some rare and serious adverse drug events, such as hemolytic anemia with temafloxacillin (49), and severe hepatotoxicity with benoxaprofen (7) and were responsible for numerous drug label changes (e.g. new warning, contraindication, ADE) and drug withdrawals from the market (48). However, these systems are generally not successful at identifying adverse drug events which are also commonly occurring problems in the general population (e.g. hypotension, myocardial infarction, depression, and cough). For example, more than 9 million people took the now infamous weight loss drug fen-phen (fenfluramine and phentermine) for off-label indications before it was identified that the drug could result in cardiac valve damage, a problem that also occurs in the general population for non-drug-related causes (7;49).

Spontaneous reporting of adverse drug events as the primary method of post-market surveillance is also plagued by other problems. These include systematic under-reporting of adverse events by physicians, lack of accurate numerators and denominators to estimate incidence, delay in detection, incomplete data on the treatment indication and age, and the lack of a relationship between reporting and prescribing (6;10-12;26;48). Although the extent to which ADEs are under-reported is difficult to quantify precisely, it was estimated that only 2-10% are reported spontaneously (6;10-12). The high rate of underreporting is not surprising considering ADE reporting by physicians is not mandatory in most jurisdictions (1;50;51). Only 63% of Canadian physicians know how to complete an ADE report, and

even fewer are familiar with where to find the ADE reporting form (1). A variety of new surveillance methods have been developed to overcome the limitations of spontaneous adverse drug event reporting.

Prescription Event Monitoring (PEM)

PEM is an active post-market surveillance method that requires physicians to respond to a follow-up questionnaire on patients' response to new drugs (52). The system uses dispensed prescriptions and collects information from physicians on patient age, treatment indication, dose, start and discontinue dates of drug treatment and the reasons for the discontinuation and any occurrence of an 'event' on and off drug. These events include new diagnoses, reason for admission to hospital, pregnancy, and death and whether the physician considers the event to be an adverse drug reaction. Incidence densities are calculated using drug events reported by the physicians as numerator and the total patient-months as denominator. In a head-to-head comparison with spontaneous reporting method, 94% of events detected by PEM were not detected by the latter (12). PEM has been implemented in the UK since 1980, and is currently being used in New Zealand, Japan and Ghana (53-55). The Drug Safety Research in the UK has completed more than 100 studies with a median cohort size of 11680 in order to study the safety of new classes of drugs such as drugs for erectile dysfunction and selective cyclooxygenase inhibitors (56;57). The PEM questionnaire was recently modified (Modified PEM) to accommodate detailed documentation of comorbidities, potential confounders and outcomes to increase the scope of the studies and address risk management questions (58).

Although the reporting rate is better in PEM than spontaneous reporting, the response rate of physicians to follow-up questionnaires was on average 52.8% (range 35%-65%) and decreased to 27.6% when information was sought for more than 30 patients from a single physician (14;52). In a study on Vioxx, the effective response rate of physicians was 36% and as much as 38% of treatment indication data was missing (59) and 39% of treatment indications were not specified in a study on montelukast (60). Moreover, physicians who prescribe new drugs to more patients are generally poor responders (61). Whereas mandatory reporting could reduce response bias, 45% of physicians are opposed to such reporting as it would increase administrative burden. Neither spontaneous reporting nor PEM are aligned

with the day-to-day activities of physicians, especially those of primary care physicians, who are responsible for the majority of prescriptions written (45). Even when mandatory reporting is instituted, such as infectious disease reporting for public health, response rates are notoriously poor (62). As a result, public health mandatory reporting is increasingly being supplemented by secondary use of automated computerized information sources such as diagnostic data from laboratory, emergency room, and medical service claims systems where richer, more reliable and timely data are retrieved (63-66).

Computerized Administrative Data

Public health research has pioneered methods for surveillance through the secondary use of computerized health data (64). The major advantage of these methods is that data are produced, almost in real-time, as a by-product of the care delivery and administrative process, without added documentation that is required in standard reporting systems. In Canada, there is the added advantage of having population-level health administrative data, where all adverse events in the population can be monitored, regardless of employment or insurance status. Owing to universal health coverage, information from the registered person database, provincial drug insurance claims database, medical services claims database, and hospital discharge abstract database can be used to create longitudinal health histories by linking data at the patient and physician levels using encrypted unique identifiers (67). The Saskatchewan and British Columbia databases also cover more than 95% of all prescriptions regardless of the payer while others (e.g. Ontario, Quebec) cover only drugs paid by the provincial government. The availability of this rich resource has allowed Canadian scientists in six of the provinces (British Columbia, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia) to advance a new generation of methods to conduct comparative observational studies to assess drug safety and effectiveness of prescription drugs after their approval (68). Although these data are collected to manage the health care system, the validity of diagnostic and prescription information for safety and effectiveness evaluation has been shown to be good to excellent (69-72). Positive predictive value for adverse event detection ranges from 73 to 99% in different studies (73;74). While the sensitivity and specificity of using computerized health administrative data for ADE monitoring has not been ascertained, these data are most representative of "real world" documentation on patterns and outcomes of drug use in the population. For example, an increased risk of hypoglycemia with gatifloxacin

was identified using administrative databases in Ontario (75), while an increased risk of death due to beta-agonists in asthma was found using databases in Saskatchewan (76). Indeed, Canadian scientists, regulators, and provincial drug benefits managers have created a Drug Safety and Effectiveness Network to allow these data to be used for monitoring safety and effectiveness (77), a proposition that has received government funding in 2009. The U.S. has already established a network for conducting "real-world" safety and effectiveness assessment (78). The Medicaid/Medicaid databases under the Center for Medicaid and Medicare currently covers approximately 50.3 million Medicaid recipients and 47 million elderly and was used for numerous studies (79-81).

Recent developments in the field of pharmacoepidemiology ushers in the creation and use of mega computerized health administrative data from the Netherlands with a coverage of 46% of population (6.7 million) and in the Nordic countries where more than 68% of the 25 million population (17 million) were include for drug utilization and ADE studies (82-84).

While administrative data have considerable untapped potential for safety and effectiveness assessment, they also have important limitations. The databases lack important clinical variables that are needed for assessing indications for treatment, risk factors (e.g. smoking, exercise, and alcohol consumption), clinical outcomes, physical examination and laboratory indices (e.g. blood pressure, height, weight, HbA1c), and health outcomes (quality of life, functional status). Diagnostic data from medical archivist's abstraction and coding of the hospital chart is generally of good quality, but diagnostic codes from physician billing data have been shown to have low sensitivity, likely because only one diagnosis can be recorded for a visit (72).

Thus, for ADE detection, administrative data are probably very good for more severe ADEs that lead to emergency care or hospitalization, but lack sensitivity for early detection of mild to moderate events. Ideally, a systematic method of capturing ADEs in the ambulatory setting would provide more comprehensive assessment, and possible earlier detection of drug-related problems. The evolution of computerized drug management and electronic health records in primary care may provide a means of addressing both of these issues:

systematic collection of important clinical variables, and a comprehensive and timely capture of ADE in ambulatory practice.

Electronic Health Records (EHR)

The twenty-first century has witnessed slow but steady in-roads in the implementation of information technologies in health care. Europe, Scandinavia, New Zealand, Australia and England have led the introduction of electronic health records in primary care (85;86). In England, one by-product of these early investments is the creation of new information sources that can be used to conduct drug safety and effectiveness evaluation. The General Practice Research Database (GPRD), which was recently named Clinical Practice Research Datalink, collects information from the electronic health records of more than 636 general practices in England at the point of care and covers approximately 5.2 million active patients (87). Similar to paper medical records, these electronic files include information on prescribed drugs, consultations, morbidity events (diagnosis and symptoms), and lifestyle (smoking, alcohol, height and weight). Over 900 studies have been conducted using the GPRD. Indeed, the availability of detailed clinical data within the GPRD allowed a sentinel study to be conducted that assessed the safety of childhood vaccines in relationship to the suspected link to autism (88). While the GPRD illustrates the potential of EHR information for safety and effectiveness evaluation, it does not have the advantages of more recently developed health technologies as 30% of data is entered as unstructured text, and information on drugs dispensed and laboratory results must be entered manually.

Another EMR used for pharmacoepidemiologic study is the Kaiser Permanente (KP) database. The KP database depends on a system of electronic medical records compiled since late 1960s to monitor adverse drug events in collaboration with the US FDA. Currently, it has 8.5 million active and 20 million past participants in its insurance scheme. The system has a number of advantages in relation to the conduct of pharmacoepidemiology studies including clinical encounter data, pharmacy data and disease registries and easy access to primary data for validation (89). Moreover, KP members are similar to the general population in race/ethnicity with the exception of white non-Hispanics, the poor and the rich, all of whom are under-represented (90). Weaknesses of the KP database include lack of important confounders (smoking, alcohol history), inability to study some drugs due to

formulary-restriction and lack of confirmed diagnoses data. Notable studies using this database include the creation of simple score method to predict the risk of warfarin-associated hemorrhage in atrial fibrillation patients and the association of early treatment of HIV and reduction in cancer burden (91;92).

The US department of Veteran Affairs (VA) health care database collects information on prescriptions and dispensed medication using a computerized system called the Veterans Health Information Systems and Technology Architecture (VISTA) (93). Linkage between VISTA and the national VA drug formulary and the VA in-patient and out-patient health care utilization databases have created an unprecedented opportunity for pharmacoepidemiologic and cost-effectiveness research using patient-level medication dispensation, medical encounter and cost data both in the in-patient and out-patient settings with more than 5.3 million population (94). A study using this database was one of the first to show the cost effectiveness of combination antiretroviral treatments (95); other notable studies include the association between simvastatin use and dementia (96) and poor medication adherence in depressed patients (97).

New Initiatives in Canada, US and Europe

New initiatives in active surveillance of the safety of drugs are being undertaken to augment current methods of pharmacosurveillance.

Drug Safety and Effectiveness Network (DSEN)

Canadian scientists, regulators, and provincial drug benefits managers have created a Drug Safety and Effectiveness Network (DSEN) to study the long-term safety and effectiveness of drugs using the population-level health administrative data to inform regulators, policy-makers, health care providers and consumers (77). This independent body connects researchers, sets research agenda and addresses drug issues raised by decision-makers (98). Collaborative centers and research teams have been set up with more than 150 researchers and the network include collaborating centers such as Canadian Network for Observational Drug Effect Studies, active surveillance, pharmacogenomics of adverse drug reactions and comparative effectiveness (99).

The 'Mini'-sentinel

This program of active surveillance of drugs was launched to address US FDA 2007 ACT to rapidly respond to safety concerns of drugs and enhance passive surveillance of drugs especially to study i) the effects of drugs in subgroups not covered by RCT (elderly, pregnant, children), ii) longer term drug effects and iii) commonly occurring outcomes not reported by spontaneous reporting method (e.g. myocardial infarction) by assembling large electronic health records from variety of sources. The mini-sentinel currently involves 17 partner data custodians including the US center for Medicare and Medicaid services, the VA, Department of Defense, Universities and private bodies and it covers 99 million individuals, 300 million person-years follow-up data, 2.4 billion unique medical encounters, 2.9 billion dispensed prescriptions, 38 million acute in-patient hospital stays and accumulating every day (100). A number of research protocols were written to investigate signals (rotaV, intussusception; saxagliptin and myocardial infarction).

Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge (EU-ADR) project

The aim of EU-ADR project is the early detection of ADE and to supplement current pharmacosurveillance methods. The data source for EU-ADR is EHRs from over 30 million patients of 8 European established EHR located in the Netherlands, Denmark, United Kingdom, and Italy (101). The system uses a distributed analyses whereby event definition, standardization and mapping of events are done at individual sites using specialized software and an aggregated and de-identified encrypted data is sent to a central statistical center for analysis. ADE Signals (drug-suspected ADE combinations) are generated from this massive EHR using data mining and epidemiological techniques. Biomedical informatics and molecular knowledge are used to elucidate mechanism of actions of drug-ADE associations. This system was compared with the US spontaneous reporting system and the WHO VigiBase (global drug safety report system) databases and was shown to complement these traditional databases to investigate high frequency adverse events occurring in the general population (e.g. myocardial infarction) (102). In addition, it was demonstrated that the data can be used for large number of drugs including infrequently used drugs and rare outcomes if network size is increased or the follow-up time is prolonged (103).

The ASTER Project (ADE Spontaneous Triggered Event Reporting)

This is a proof-of-concept project completed in 2008 with the aim to automate ADE reporting from EHR (Partners Healthcare) in collaboration with public and private organizations (46). A trigger is initiated when a physician discontinued a drug due to an ADE and a report form within the EHR is presented to the physician pre-populated with comorbidities, drugs, weight/height and lab values. The physician completes the remaining fields and releases the form to a company which formats the electronic report and sends it to the FDA. The pilot project involved 26 physicians and 217 ADE reports were submitted to the FDA within 5 months. Completing and sending the form on average took 53 seconds, a 40-fold decrease in documentation time compared to completing the standard form (104). The pre-populated forms had information on comorbidities (95%), medications (89%), lab values (99%), and weight and height information (89% and 82%, respectively). The majority of the physicians (96%) felt the system would increase their ADE reporting. The system was heralded as a first step in bringing spontaneous reporting to the electronic age (104).

Off-label prescribing and use

The origin of the drug label

Drugs must pass rigorous scrutiny before they receive approval for marketing in accordance with requirements of the *Food and Drug Act and Regulations* (Canada). These include preclinical studies on cells and animals and three phases of clinical trials on humans that culminate in an application to a drug regulatory body (e.g. Health Canada or US FDA). A new drug submission (NDS) should include the preclinical and clinical information pertaining to safety, effectiveness and quality of the product (Health Canada). The therapeutic product directorate (TPD) and the center for drug evaluation and research (CDER) under Health Canada and US FDA, respectively, are tasked with analyzing this document supplied by the sponsor of the drug (e.g. pharmaceutical company) and deciding whether the benefit of the drug justifies the risk associated with the use of the drug and whether the risk can be mitigated. Drugs are specifically evaluated in relationship with the treatment indication(s) in which they were tested since efficacy is tied to a disease condition and safety needs to be demonstrated for the specified indication(s). A satisfactory review of a drug submission results in an issuance of a notice of compliance (NOC) and drug identification number (DIN) which allows the

pharmaceutical company to market the drug in Canada (105). Health Canada and the pharmaceutical company negotiate the terms of reference that will be used to describe the drug's safety and effectiveness, based on information in the document originally supplied by the company. The drug label or product label (or drug monograph) contains these agreed upon terms including the treatment indication, dosage of the new drug, the population for which the drug can be prescribed, contraindications, side effects, cautions and other pertinent information which are important to inform (but not advertise to) health care professionals for the safe use of the drug. In order for pharmaceutical companies to modify these terms, they must submit a new supplemental drug submission (SNDS) and obtain an approval to include, for example, new indications or new user groups (e.g. children) in the product label. In 1998, a second category of NOC called notice of compliance with condition (NOC/c) was created to expedite market entry of drugs for serious, life threatening or debilitating illnesses such as HIV/AIDS (106). The 'with condition' term involves additional post-marketing commitments made by the company including execution of confirmatory trials and monitoring of safety issues.

In recent years, drug regulatory bodies have been creating mechanisms (e.g. priority review) to expedite the drug review process and allow rapid access of drugs to the public. The effect of these new processes is still being debated, and its impact on the number of drug withdrawals and public safety is being monitored (7;107;108). The move to proactive risk management and benefit-risk analysis of drugs is gaining more traction than the customary more precautionary and passive approaches to risk management (109) due in part to the Vioxx disaster and recommendations from the Institute of Medicine (IOM) on drug safety (110). As a result, a number of jurisdictions (Europe Union – European Medicines Agency Road Map Initiative; USA – Food and Drug Administration Amendments Act of 2007 and Canada - Progressive licensing framework for drug approval) have mandated the life-cycle approach to drug evaluation with its greater emphasis on ongoing pharmacovigilance than traditional pre-marketing approval which reflects a point-in-time model (109;111). The principle of the life-cycle approach includes specific commitments for post-marketing studies and risk management plans at the time of drug submission and evaluation.

Off-label: definition

Once a drug is approved for marketing, physicians can prescribe the drug for any treatment indication or patient group, including indications and populations that are not included in the product label or the drug label. Off-label use is defined as the use of a prescription drug for an indication, in a dosage form, dose regimen, or for a particular population not covered by the approved labeling where safety and effectiveness were assessed (17). Most studies on off-label use consider the indication and the population components of the definition while disregarding the doses or route of administration due in part to the lack of usable data and the fact that deviation from on-label uses is not that extreme. As a result, there is a need to describe the definition used for off-label use and the population under study before comparing prevalence of off-label use.

Off-label use and drug regulatory bodies

Generally, Health Canada plays a hands-off approach in the direct regulation of off-label use, leaving this task to the provinces, physician professional associations and sometimes to the courts (112). However as part of its mandate in pharmacosurveillance and due to public pressure, Health Canada was forced to respond to some major safety issues involving off-label use of antidepressants in children (113;114). Depending on the risk associated with an off-label use, Health Canada may request the drug company to include a caution or a contraindication in the product label of the drug (112). These requests are most often directed towards off-label use in children where such practices are easier to identify (115).

Off-label drug promotion is prohibited in Canada according to the *Food and Drug Regulation.* Health Canada has a mandate to regulate drug promotion with the help of the Pharmaceutical Advertising and Advisory Board (PAAB), a body made up of the pharmaceutical industry, the medical and pharmacy associations, consumer groups, the advertising industry and Health Canada (as an observer) (116). The task of PAAB is mainly preclearance review of health product advertising, aimed at health professionals or consumers, and voluntarily submitted by the drug industry. Pharmaceutical industry-sponsored symposia or press releases speculating on an off-label uses were among the venues not identified as advertising by Health Canada (117), and sometimes may not be cleared by PAAB, creating a potential loop-hole for promotion of unapproved uses of drugs (112;118). While Canada uses a mixed system of regulation, the US uses direct government

control and others (Australia, the UK) use self-regulation by the pharmaceutical industry. Unlike Canada, the US allows dissemination of peer-reviewed articles from scientific journals on off-label uses since 1997 (119). In the era of ghostwriting of journal articles, "seeding trials" for marketing with extensive publication planning by the pharmaceutical industry and the conflict of interest between journals and the industry (120), the merits of 'peer-reviewed' publication were called into question (119;121). In the last decade, federal and state prosecutors in the US had managed to file criminal and civil charges using provisions like 'misbranding' (when the drug label contains misleading information including information about unapproved uses) and the False Claim Act resulting in more than 13 billions of dollars in fines (119). As a result, US courts became major players in setting rules involving off-label marketing.

Off-label use and the patient

In a survey of US adults, as much as 45% of the population feels physicians should not be allowed to prescribe off-label, however the same percentage is in favor of allowing physicians to prescribe off-label. Survey respondents' position towards the pharmaceutical companies was even stronger with 73% indicating that drug companies should not be allowed to encourage doctors to prescribe off-label (122). Patients with life threatening diseases naturally support off-label use since it allows rapid access to potentially "effective treatment". Cancer, HIV/AIDS and orphan diseases have a higher prevalence of off-label use (123-126). Moreover, patients were known to self-experiment with unproven treatments for conditions such as amyotrophic lateral sclerosis (127;128). The experience of patients using off-label drugs were chronicled through online communities like PatientsLikeMe and include diagnoses, drug effectiveness and side effect profiles (127;129). Patient advocacy groups, patients and family members are the first to demand off-label use of drugs (130). For example, physicians received calls from family members of Alzheimer's patients for an off-label use of a skin cancer drug after the drug was shown to clear plaques from the brain of Alzheimer's disease in mice models (131). When fatalities due to off-label use of drugs occurs, the public and the media are typically incensed about why this has happened, questioning the potential failure to intercede by drug regulatory bodies (Health Canada)(132). For example, a coroner's report (114) on the death of a 6-year-old girl (Ashley Atkinson)

who had died due to complication of pneumonia and who also had an exposure to an off-label drug had strong recommendation for reform in off-label surveillance to Health Canada:

> "Health Canada must formally acknowledge and recognize off-label usage of regulated pharmaceuticals and must formally monitor that usage notwithstanding the fact that the approval for the usage has never been obtained from Health Canada."

In this particular case, Health Canada's response did not directly address the issue of off-label use; stating that adverse drug reactions were monitored irrespective of on- or off-label use despite under-reporting with traditional methods and lack of specificity with respect to treatment indication. Health Canada verified the lack of jurisdiction over how physicians prescribe drugs. However, current regulations do not prevent Health Canada from assuming responsibility for monitoring drug uses as part of its lifecycle model, be it on-label or off-label.

Off-label use and the Pharmaceutical industry

Drug development is an expensive process but the exact dollar figures are disputed (133;134) by various experts. According to one estimate, it costs the pharmaceutical industry from 800 million to one billion dollars to bring a single drug to market but this amount included the cost of other drugs which did not make it to the market (135). As a result, companies are given exclusive rights to sell their drugs for specified number of years. Sales generated from the approved drugs must cover the research and developments cost and generate profit for the shareholders within the market exclusivity period. Because, the patent owners lose from 44% to 81% of market share of the brand-name drug within first year of generic drug entry or a loss of 87% for drugs with annual sales more than 100 million (136), the pharmaceutical industry are using patent infringement court proceedings and stays ("ever greening") to extend their market exclusivity for as much as 8 years after the expiration of their patent (137-139). For the pharmaceutical industry, the role of off-label use and marketing are played in the background of cost of drug development, market exclusivity, patent expiry date and loss of income.

In most jurisdictions, pharmaceutical companies are not permitted to advertise drugs for off-label treatment indication (US, Canada). However, in the past 8 years, the pharmaceutical

companies paid more than 13 billion dollars to the United States government to settle unlawful promotion of drugs for unapproved indications and population.(140-142)

Three drugs, one story

The Neurontin (Gabapentin) story

Neurontin® (Gabapentin) is a poster child of off-label marketing and underscored the rewards and the ills for the pharmaceutical industry. Gabapentin is a drug approved to treat seizure disorders as an adjuvant (in US and Canada) and in 2002 for post-herpetic neuralgia (US). Pfizer (Warner-Lambert) paid 430 million dollars to the United States government in 2004 after admitting guilt for illegal promotion of gabapentin for off-label indications (143). In the same year, the sale of gabapentin reached 2.72 billion, mostly for off-label indications (144;145). Internal documents from the company made available through the litigation process were used to scrutinize activities practiced by the company related to off-label marketing of gabapentin. Drug detailing was one of the major promotional activities practiced where at least one off-label use was mentioned without stating the on-label use and 46% of the detailed physicians reported the intention to increase their prescribing of gabapentin (146). In addition, a variety of methods were used to promote the drug including accredited medical education events, recruitment of thought leaders and local champions, publishing ghost-written articles and suppressing negative study results (147). A quote, obtained as part of court document of the litigation, by a senior marketing executive of the company labeled "Neurontin for everything" shows the extent of promotional activity demanded from the company's employees.(148)

> "I want you out there every day selling Neurontin. Look this isn't just me, it's come down from Morris Plains that Neurontin is more profitable. . . . We all know Neurontin's not growing adjunctive therapy, beside that is not where the money is. Pain management, now that's money. Monotherapy, that's money. We don't want to share these patients with everybody, we want them on Neurontin only. We want their whole drug budget, not a quarter, not half, the whole thing. . . .We can't wait for them to ask, we need to get out there and tell them up front. . . .That's where we need to be holding their hand and whispering in their ear Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything. . . . I don't want to see a single patient coming off Neurontin until they have been up to at

least 4800mg/day. I don't want to hear that safety crap either, have you tried Neurontin, every one of you should take one just to see there is nothing, it's a great drug."

Pfizer is currently embroiled with more than a thousand law suits involving patients and insurers (e.g. Kaiser Permanente) alleging suicides for the drug users and racketeering charges; with some success for the plaintive (149;150). However, all the charges and the recovery of hundreds millions of dollars from the company to the United States government, patients and insurers did not result in a significant change to off-label use of the drug, according to time-series analysis using the different legal and regulatory time periods (151).

The Avastin® (bevacizumab) / Lucentis® (ranibizumab) story

Avastin and Lucentis are derived from the same monoclonal antibodies. Avastin was first approved for the treatment of metastatic colon cancer and later other cancer types (e.g. metastatic lung, glioblastoma) were included in its portfolio. Lucentis was approved in 2006 to treat-age related macular degeneration, a leading cause of vision loss in the elderly. Physicians started to use Avastin for age-related macular degeneration based on a favorable outcome in single case study (152) and a remarkable effect of Lucentis shown in RCT. Approximately 60% of patients with age-related macular degeneration were treated with Avastin due to its availability and cheap cost relative to Lucentis (50 USD vs. 2000 USD) (153), despite warnings from the manufacturer of Lucentis about the danger of off-label use of Avastin for age-related macular degeneration (154) and safety issues related to infections due to repackaging of Avastin (155). A 2011 RCT (156) concluded that the two drugs were comparable in their efficacy and a need for safety studies. According to US Inspector General report (153), the government and patients will save 1.1 billion dollars and 275 million dollars, respectively if Avastin replaces Lucentis; but spending will increase by 1.5 billion dollars for the government and 370 million dollars for the patients if the reverse happens. This case illustrates the reversal of roles for the government/patients versus the pharmaceutical company, where the government/patients benefit with off-label use and the company loses revenue if off-label use dominates the picture. This reversal of roles is related to economic decision; how to expand corporate profit vs. how to treat more people with less money.

Off-label prescribing and the physician

Physicians have broad discretion on drug prescribing including for treatment indications that have not received regulatory approval (114;157), as long as it is aimed at the best interest of the patient (158). Reasons given by physicians for off-label prescribing (159;160) include 1) class effect: the indication is approved for one drug in the drug class (e.g. captopril for diabetic nephropathy); using another drug from the same drug class (e.g. enalapril) which is not approved for the indication. 2) extension to conditions which have related symptomatology e.g. modafinil is approved for narcolepsy and its use is extended to treat fatigue in multiple sclerosis or chronic fatigue syndrome (129) 3) treating milder forms of a disease (e.g. antidepressants for dysthymia) 4) indication was *treatment guideline recommended* but not included in the label of the drug (e.g. amitriptyline for migraine prophylaxis (161)) 5) last resort - tacrolimus for autoimmune conditions 6) sharing presumed pathophysiological link (metformin for polycystic ovarian syndrome) 7) pharmaceutical company's reluctance to be associated with an indication (e.g. misoprostol for abortion) despite proven safety and effectiveness of the drug in RCTs (162) 8) orphan diseases – lack of drugs due to rarity of the disease 9) side effect of a drug (amitriptyline and dry mouth) as desirable effect for another condition (controlling excessive saliva in amyotrophic lateral sclerosis (ALS) patients) (129).

According to Eisenberg's (163) sociologic influences on clinicians' decision-making model, several factors related to the physician, the patient, the sociocultural environment and biomedical considerations play role in diagnosis and treatment. On- and off-label drug prescribing is under the full discretion of the physician and depends on how informed the physician is about drugs and their indications, their effects and side effects.

While a patient's clinical condition, and availability of efficacious drugs were cited as important determinants of off-label prescribing, the physician-related factors such as knowledge about drugs and their indications has been mostly overlooked. A study (164) in representative sample of U.S. physicians tested physicians' knowledge about FDA-approved indications for commonly prescribed drugs. The study found that the average respondent accurately identified only 55% of the on- or off-label status of the drug-indication pairs and

this accuracy was increased modestly to 60% when the analysis was limited to drugs the respondent prescribed in the past 12 months. Moreover, as much as 41% of physicians believed at least one drug-indication pair which lacked supporting evidence for its efficacy was FDA approved. Physicians' lack of knowledge on drugs and their indication was observed (165) three decade earlier where only 7 out of 10 physicians correctly identified whether indication-drug pairs were FDA-approved or not and there was no difference between staff physicians and residents in correct responses to drug-indication questions.

Eighty-eight percent of physicians considered their training and clinical experience as the most important factors that influence their prescribing behavior, giving a lesser role to colleagues and even minuscule roles to drug detailers, patients and advertisements (166). However, other studies identified additional sources of drug information for physicians' that included fellow physicians', hospital based specialists, and exposure to patients treated by other physicians either from other physicians or from hospitals (167). Issuance of drug prescription also depends on a number of factors including the diagnosis (168;169), severity of illness (169;170), the specialty of the physician (169), the sex of the physician (171-173), practice setting (171;174;175) and age (169), sex (176), race/ethnicity (172;177-179) and socioeconomic status (180) of the patient .

Physicians who received frequent visits from pharmaceutical representative were receptive to drug advertisements and promotional literatures (181), were early prescribers of new drugs (181-183), prescribed broad range of drugs and were high volume prescribers (184-186). Physicians who receive information from industry representatives believe the information on new drugs were reasonably accurate and they also acknowledge its selective nature (185). Most physicians believe they are not influenced by pharmaceutical representatives or advertisements unlike their colleagues (166;187;188) and claimed to use scientific sources in their prescription decision. However, despite these claims, they wrote drug prescriptions for scientifically unsupported commercially advertised indications, underscoring the influence of pharmaceutical industries on physicians (166). Moreover, the negative effect of pharmaceutical representatives on prescribing was shown in a number of studies (166;189-191).

Most physicians considered cost of drugs as important in their prescribing decisions (192-194). As much as 71% of physicians were willing to prescribe less efficacious cheaper drugs, however close to 80% of physicians were unaware of the actual cost of the drugs (195-198). Physician prescribing was associated with patient health insurance status where patients with insurance were prescribed more antidepressant drugs compared with self-paying patients for depression (169;176).

The other important factor in physicians' prescribing decisions is the demand or expectation from patients and the perception of physicians about patient expectation. Physicians ascribed close to 50% of their mis-prescribing to patient demand (199) however a fifth to half patients had received prescriptions they did not expect (200;201). This mis-match in physician and patient expectations was mostly due to the difficulty physicians experience in evaluating patients' expectation for drugs (200;202). While the patient's expectation for drugs increased the chance of receiving a drug after consultation, the chance increased by several fold if the physician perceived this expectation (183;200;202;203). For example, the odds of receiving a drug prescription was increased by three fold when the patient expected to receive a prescription and the odds increased by ten-fold when the physician perceived this patient expectation (203). Factors which played role in patient expectation include the reason for the visit and the severity of the condition (200) and 'trust in the effectiveness of drugs' (202). Fulfilling patient expectation was not without consequences since it created physician discomfort especially when antibiotics, tranquilizers, hypnotics and systematic remedies were prescribed (204).

The Epidemiology of Off-label prescribing in Primary Care setting

The definition of off-label prescribing includes the indication, dosage form, dose regimen, and population included in the product label. Most studies on off-label use consider the indication and the population components of the definition and they study a limited subset of drugs. As a result, the prevalence of off-label prescribing depends on the off-label definition used and the population and drugs included (Table 2.1). In addition, the care setting in which the study is conducted (hospital vs. primary care vs. specialty clinic) is also

an important determinant of the prevalence of off-label use since the patient population and the case-mix in these settings are diverse. This thesis deals with off-label prescribing in primary care setting where most drugs are prescribed (205;206). The sources of data for comparable primary care studies come from a number of areas that have different approaches and potential biases for the measurement of off-label prescribing, and these include: 1) periodic surveys of patient-physician encounters with (18;19;33;207;208) and without a direct link (209-213) between drug and ICD-9 codes (representing treatment indications) obtained from the physician, 2) administrative health data base, Medicaid data (81;214), where ICD-9 codes (diagnoses) and drug were obtained without any direct or temporal link between drugs and diagnoses 3) single practice settings (165;215-217) where drug and treatment indication data was retrieved from the patient chart and 4) electronic health record (205;218), where there is no direct link between drugs prescribed and the problem list except a co-occurrence in the patient's chart.

The first land mark study (Strom *et al* (19)) which evaluated off-label prescribing in the primary care setting included both adult and children and used the National Disease and Therapeutic Index (NDTI) data collected from 1500 out of 199,000 randomly selected primary care physicians in 1978. One hundred of the most common drug uses for drugs approved by FDA (post-1963 approved drugs) were evaluated. The definition of off-label prescribing included treatment indications, contraindications and efficacy of the drug for a particular indication. This study estimated the prevalence of off-label prescribing as 31% at the time of drug marketing and this prevalence went down to 18% when some new indications were approved by the FDA and included in the drug label. This is the first study which posited the need for post-marketing studies of drug efficacy for off-label uses.

The second landmark study of off-label prescribing in primary care, Radley *et al* (18), also used NDTI data (2001) and included 403,975 patient-physician encounters. Each quarter 3,500 United States office-based physicians were selected using random stratified sampling to report on two randomly selected workdays on their clinical activity based on a list of activities from the American Medical Association and American Osteopathic Association. All drugs used to treat each patient's diagnosis(es) were recorded and included prevalent and incident drugs prescribed in the patient's encounter. While the NDTI data contain the top

500 drugs by frequency, this study included 160 drugs, the top 100 drugs by frequency and 60 randomly selected drugs, which accounted for 56% of the prescriptions. Diagnoses were coded using ICD-9-CM codes. Drug-indication (ICD-9 code) pairs were grouped into on- or off-label prescriptions using the therapeutic indications in the drug package insert (Physician Desk Reference, 2002). DRUGDEX was used to evaluate the strength of evidence for off-label uses as having strong or little/no scientific evidence. The study reported a 21% prevalence of off-label prescribing, 73% of which lacked strong scientific evidence for the off-label use. Higher percentage of off-label prescribing was reported for anticonvulsants (46%), psychiatric (31%) and antimicrobial drugs (23%). The drugs with highest prevalence of off-label use include gabapentin (83%), amitriptyline (81%), dexamethasone (79%), risperidone (66%) and temazepam (63%). *Drug class* and *number of approved indications* were associated with off-label prescriptions. The association with number of approved indications was counterintuitive since it implies that drugs with more approved indications had more off-label use. A number of drug-related factors including manufacturer, drug age, degree of direct-to-consumer promotion, use as long term therapy, medication form, frequency of use and generic availability were investigated however no significant association with off-label prescribing was identified. The study raised important questions which have drug policy implication such as the type of data needed to inform the clinical and economic implication of off-label use and how and when this data is analyzed and reported in relation to new drug market entry. The study has a number of limitations. First, due to proprietary nature of the data, the specific information on sampling methodology, sample size, eligible physicians and response rate was limited, calling into question the representativeness of the physicians and by extension the patients to the United States population and the validity and the reliability of the data (219). Second, the reported off-label prevalence did not represent the 44% of drugs not included in the study. Third, measurement error is introduced by the difficulty in mapping treatment indications captured as ICD-9 codes and treatment indications approved by FDA due to terminology difference and imprecision of diagnoses. Fourth, the classification of off-label use into off-label use with and without scientific evidence was described with insufficient detail to allow evaluation of the criteria. Fifth, there might be over-representation of patients with more comorbid conditions owing to the fact that the NDTI is based on patient visits (208). In conclusion, this is the first study which brought the

issue of off-label prescribing to the forefront and advocated for mandatory surveillance of off-label uses especially the ones which lacked scientific support.

As a follow-up to Radley *et al*, Walton *et al (33)* investigated off-label prescribing in 2005-2007 using NDTI data, which included all drugs except anti-neoplastic and vaccines prescribed for adults. The aim of the study was to create a prioritization index to study individual drugs or class of drugs for future studies of off-label use. The drug prioritizing index combined volume of off-label, quality of evidence for off-label use, safety of the drug, and a composite scale representing cost, recency of market entry and degree of marketing. Drug classes which were assigned higher priority for future studies include antidepressants, antipsychotics and anxiolytic/sedatives and the drugs included quetiapine, warfarin, escitalopram, risperidone, and montelukast. The following drugs were reported to have the highest off-label use: gabapentin (93.4%), promethazine (92.9%), clonazepam (76.6%), quetiapine (75.4%) and amitriptyline (69.3%). This study suffers the same limitation as the prior Radley *et al* study with the exception of the evaluation of scientific evidence where the classification of off-label use was explicitly described allowing evaluation of the method and ensured reproducibility by other researchers (208).

Alexander *et al* (208) investigated the trend in off-label prescribing of typical and atypical antipsychotics using three years of NDTI data (1995, 2006 and 2008) and reported increased use of antipsychotics, a marked shift from typical to atypical antipsychotics, and a more than double increase in off-label uses. The majority of this increase was due to growing use among 18-65 years adults for off-label indications which lacked strong scientific evidence. Moreover, the estimated cost of antipsychotics in 2008 was $6 billion, of which 90% was for uses which lacked strong scientific evidence. This study demonstrated the exponential growth of atypical antipsychotics, replacing typical antipsychotics and expanding into the treatment of bipolar disorders and depression where their effectiveness and safety data is limited. The study has the same limitation as Radley *et al* (18) and Walton *et al* (33).

Off-label prescribing is a contentious issue that involves the general public which is why it was part of a Knight Ridder special investigation (207). The reporters used Verispan (Yardley, Pa) data which collects prescribing information from 3,400 physicians every month

Table 2.1 Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Strom *et al.*,1985 (19)	NDTI – a rotating panel of over 1500 physician (out of a total of 199,000) report four times a year on contacts with patients' during a 48-hour period. (Adult and children, USA, 1978)	All drug except the ones approved before 1963 (not subjected to US FDA requirement)	Treatment indication, contraindications and efficacy were considered	100 most common uses (drug-indication pair) Proportion of not-approved drug-indication pair.	31 of the 100 most common uses were treated off-label at the time of initial marketing. 18 had not become US FDA-approved subsequently. 8 were known to be ineffective for the indication.	Representativeness was limited since the projected annual prescription volume for the 100 uses represented only 10% of the total prescriptions.
Radley *et al.*, 2005, (18)	The 2001 National Disease and Therapeutic Index (NDTI) Adult and children in primary care (USA)	Top 100 and 60 randomly selected drugs representing 56% of all prescriptions in 2001.	Only diagnosis (indication) was considered. Off-label use was categorized into with and without strong scientific evidence using DRUGDEX© system.	Proportion of off-label mention. Predictors of off-label use: functional class, drug age, manufacturer, degree of promotion, use as a long-term therapy, medication form, frequency of use, generic availability, number of approved indications	Off-label use: 21%; of which 73% lacked strong scientific support. Substantial variation in off-label by functional class. - Cardiac and anticonvulsant: 46% - Antimicrobials: 23% - Psychiatric (antidepressant, anxiolytic and antipsychotics): 31% Specific drugs: - Gabapentin: 83% - Amitriptyline 81% - Dexamethasone: 79% - Risperidone: 66% - Temazepam: 63% Predictors of off-label use: - Number of approved indication: OR = 1.03 (1.01, 1.05)	Representativeness is limited since 44% of drugs were not investigated. No comment can be given on the representativeness of the physicians included in the survey since response rate was not reported.

NDTI - National Disease and Therapeutic Index; FDA – Food and drug administration

Table 2.1 (Continued) Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Walton *et al.*, 2008 (33)	NDTI, 2005 - 2007 (2 1/2 years), USA Only adults were included.	All drugs except chemotherapeutic agents and vaccines.	Only indications were considered.	Prevalence of off-label by drug. Prevalence of off-label without strong scientific evidence. An index to prioritize drugs for future studies which combines volume of off-label, quality of evidence for off-label use, safety of the drug, and a composite scale representing cost, recency of market entry and degree of marketing.	Highest off-label - Gabapentin: 93.4% - Promethazine: 92.9% - Clonazepam: 76.6% - Quetiapine: 75.4% - Amitriptyline: 69.3% Low scientific evidence for off-label use: Promethazine, clonazepam, quetiapine & gabapentin. Priority drugs rank by index: - quetiapine, warfarin, escitalopram, risperidone, montelukast Priority drug classes: - antidepressants, antipsychotics and anxiolytic/sedatives	Misclassification of off-label status: the evaluation was ICD-9 based with little or no verification of codes and drugs and differences in terminology between ICD-9 codes and indications listed by FDA. Representativeness of the result was questionable since the sample of physicians was not strictly random (past respondents may continue to participate while drop-out physicians were replaced by new ones)
Alexander *et al.*, 2011 (208)	NDTI, – a rotating panel of 4800 physician report four times a year on all contacts with patients' during a 48-hour period (USA, 1995, 2006 and 2008)	Typical and atypical anti-psychotics	Only indications were considered.	Trends in antipsychotic use Off-label trends stratified by typical and atypical antipsychotic group	Increased in antipsychotic use from 6.2 million to 16.7 million visits. A shift from typical agents (84% of 1995) to atypical agents (93% of 2008). Off-label antipsychotic use doubled from 1995 to 2008. In 2008, 60% of visits were off-label. The majority of increase in off-label use was due to increasing use among 18-65 years adults for off-label use without strong scientific evidence. The estimated cost of antipsychotics in 2008 which lacked strong scientific evidence was $5.4 billion.	ICD-9 based method with little verification of codes and drugs.

Table 2.1 (Continued) Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Young *et al.*, 2003 (207)	Prescribing information collected by Verispan of Yardley, Pa., from a monthly survey of 3,400 doctors with office-based practices (1998 and 2003, USA)	The three top selling drug from 15 drug classes	Only indications were considered.	Prevalence of off-label use: overall, by drug class and drugs. Serious ADR reports to the FDA due to off-label uses	Off-label (overall): 21% Drug Class: - Anticonvulsants: 74% - Antipsychotics: 60% - Antidepressants: 40% - COX-2 inhibitors: 17% - Cholesterol lowering: 4% - Diabetes: 3% Specific drugs: - Gabapentin: 90% - Quetiapine: 78% - Risperidone: 65% - Trazadone: 56% - Azithromycin: 45% - Olanzapine: 42% Cost of off-label: 12.9 billion (30.3% of the total drug cost) Harm report to FDA due to off-label use: 800 reports of serious ADR in 2002 from 45 drugs.	Method looked similar to NDTI, however details were lacking from the reports.
Lin *et al.*, 2006 (212)	The National Ambulatory Medical Care Survey (NAMCS) collects health care resource utilization data in the US. (1999 to 2002).	All visits with one or more β-blockers was prescribed were used	Only indication was considered.	The trend in off-label β-blockers use Contributing factors of off-label use	Off-label use = 52% - Atenolol = 51.3% - Metoprolol = 52.9% - Propranolol = 59.5% Significant predictors of off-label use: OR - older age, 0.99 - female, 0.74 - # of drugs, 1.13 - specialist (vs general practitioner), 2.14	Misclassification bias was high since only 3 diagnoses and 6 drugs were captured per visit and there was no link between drugs and indications.

NDTI - National Disease and Therapeutic Index; NAMCS - The National Ambulatory Medical Care Survey;

Table 2.1 (Continued) Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Sugarman *et al.*, 2002 (211)	NAMCS, 1990 to 1997, USA	Drugs for the leading 10 dermatologic conditions for which medication are indicated.	Only indications were considered.	Prevalence of off-label use	Off-label prevalence for 10 leading dermatologic conditions: 32%; range (17%, 73%) - for dermatologist:24% - for others: 34% Highest off-label drug use: - acne rosacea (73%); actinic keratosis, (52%) Lowest off-label use: - atopic dermatitis (17%); psoriasis (16%)	Misclassification was possible since only 3 diagnoses and 6 drugs were captured per visit and there was no direct link between the drug and the indication.
Lai *et al.*, 2011 (210)	The NAMCS data of 2006 with at least one insomnia drug prescribed was used for this study.	On-label drugs for insomnia: benzodiazepines and selective melatonin receptor agonist (ramelteon). Off-label: antidepressants (trazodone, amitriptyline, nortriptyline and mirtazapine).	Patients with ICD-9-CM code for depression were excluded.	Prevalence of insomnia treatment with off-label (antidepressant drugs) Risk factors: Age, sex, ethnicity, insurance type, physician speciality, office setting, office ownership.	Off-label treatment of insomnia: 45.1% - trazodone (17.9%), amitriptyline (14.5%), mirtazapine (5.8%), nortriptyline (4.7%), doxepin (2.3%) Significant predictors of off-label use: - self-paying patient: OR, 2.6 - urgent centers: OR,3.3 - pediatricians: OR, 65.9 - neurologist: OR, 4.8 Patient age, sex and ethnicity were not predictors of off-label use of antidepressants for insomnia.	Only patients with depression diagnosis were excluded from the off-label group. Other indications where an antidepressant was used as an on-label treatment was retained. This clearly inflates the off-label use of antidepressants for insomnia since the antidepressants could be used for other on-label and off-label indications i.e. lack of depression diagnosis does not equate with insomnia diagnosis. (flawed study design)

NAMCS - The National Ambulatory Medical Care Survey

Table 2.1 (Continued) Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Pearce *et al.*, 2006 (209)	The NAMCS data from 1994 to 2002 where calcipotriene was mentioned.	Only one drug was included: calcipotriene	All patient with a mention of calcipotriene	Prevalence of off-label use and trends of calcipotriene use	Off-label: 57% A rapid rise in calcipotriene use immediately after approval in 1994 and a rapid decline in use in 1998. The rapid rise and fall followed off-label use, prescribing by non-dermatologist physicians, use by female and white patients.	Misclassification of off-label use since lack of psoriasis was considered as off-label use and there is no validation to prove this and unexpected high rate of vulvo-vaginitis due to similarities of ICD-9 codes with psoriasis was noted.
Chen *et al.*, 2005 (81)	State of Georgia Medicaid eligible population from outpatient (>90%) including < 18 years olds (16%), (1999 – 2000, USA)	Only anticonvulsants were included	Indication and age were considered. Prescription of one anticonvulsant for a drug approved to be an adjuvant was also considered off-label. Evidence-based off-label: an off-label use supported by at least one RCT or validated by Cochran review.	Off-label and evidence-based off-label proportions. Identify patient and physician characteristics associated off-label prescribing	71.3% of 48,648 patients on anticonvulsant were used to treat off-label condition. 96% of the off-label uses were classified as off-label using the indication criterion alone. From 19-57% of the off-label uses, there is no RCT performed. Higher prevalence of off-label use in drugs marketed after 1993. Highest prevalence of off-label: - Gabapentin: 86% - Lorazepam: 80.3% - Diazepam: 72.7% Predictors of off-label: - Elderly had the lowest chance of receiving an off-label drug. - Females, non-whites and patients with depression, pain and epilepsy had higher chance of receiving an off-label drug.	Lack of link between drug and indication might have underestimate or overestimate the prevalence of off-label prescribing. Treatment indications were coded with ICD-9 creating non-specificity of indications which in turn might affect the prevalence of off-label. Evidence evaluation of off-label use was suboptimal since it required only one RCT without any condition for the quality of the RCT. Generalizability to the larger patient population is restricted since only 65% of Medicaid enrollees were included.

NAMCS - The National Ambulatory Medical Care Survey

Table 2.1 (Continued) Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Chen *et al.*, 2006 (214)	Georgia Medicaid administrative claim database, 2001, Adult, USA	Antidepressant, anticonvulsant, and antipsychotic medications	Only indications were considered.	Prevalence of off-label use for the three drug classes and drugs	Off-label by drug Class: - Anticonvulsants (80%), - Antipsychotics: 63.6% - Antidepressants: 75.4% Off-label (%): - Amitriptyline: 81.3% - Paroxetine: 66.9% - Trazadone: 65.6% - Gabapentin: 98.0% - Lorazepam: 88.6% - Risperidone: 66.8% - Quetiapine: 59.3% - Olanzapine: 51.7% Predictors of off-label use: - > 65years, white race, new anticonvulsant, speciality, renal failure, major depression, mental retardation, Alzheimer's disease, neurologic disorder, psychosis, schizophrenia and pain problems.	Identification of treatment indication depended on availability of ICD-9 codes which might have resulted in overestimation of off-label rate due to under- and mis-coding.
Gijsen *et al.*, 2009 (205)	Nationally representative network of 85 general practices in the Netherlands. (Adult and children)	48 ill-founded (uncertain or inadequate evidence) off-label uses using pharmacotherapeutic and clinical practice guidelines	Only indications were considered. - ill-founded off-label: not in the label of the drug, not recommended in pharmacotherapeutic books, not recommended by Dutch clinical practice guidelines	Ill-founded off-label uses in 48 selected drug-indication combinations; with a prevalence of 1/1000 persons and that can be operationalized using ICPC and ATC.	Only 25 of the 48 ill-founded off-label uses were identified. Only 0.9% of prescriptions were ill-founded off-label uses. The top four drugs and indication pairs with off-label use: betahistine (dizziness), etoricoxib and celecoxib (back pain), and amitriptyline (headache). 5% of olanzapine and 10% of risperidone were prescribed for ill-founded off-label uses (ADHD, antisocial behaviour).	For more than a quarter of the prescriptions (27.6%), no ICPC (diagnosis) code was assigned and this might have resulted in underestimation of off-label use if lack of code was associated with off-label indication. Lack of link between drug and indication made the determination of off-label status difficult. The treatment indications were not validated.

Table 2.1 (Continued) Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Rijcken *et al.*, 2003 (216)	Local health center in the northern Netherland (1996 – 1998) A retrospective study where patients with antipsychotics were identified and physicians were asked about the diagnosis.	All antipsychotic medication except lithium as mono-therapy	Only indications were considered with an addition of a third category in the label classification: quasi-label (off-label indication with psychosis as an inherent comorbidity)	Prevalence of quasi-label and off-label use	Quasi- and off-label uses in males (33.2%) was more than female patients (20%) A hospital psychiatrist was the diagnosing physician and drug prescriber in 63.9% of males and 69.4% of females.	Some of the quasi-label groups should be grouped under on-label as a result on-label prescribing was underestimated. Limited generalizability since patients from only four general practitioners was included.
Weiss *et al.*, 2000 (217)	Patient who had their antipsychotic prescription filled at three local pharmacies and who consented for interview in 1996 and 1997. (Austria)	All antipsychotics drugs	Only indications were considered - indications outside of schizophrenia were defined as off-label	Prevalence of off-label Risk factors: - age, gender, education, duration of treatment, efficacy of treatment, marital status,	Off-label use: 66.5% Older patients, unmarried or divorced got more off-label. Patients with on-label use experienced more side effects than patients with off-label use.	Number of eligible patients or the response rate was not reported. Indications for treatment were obtained from patients and this might have created a misclassification since patients might not know the exact diagnoses or under-report diagnosis of psychosis for fear a stigma.

Table 2.1 (Continued) Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Conti *et al*., 2011 (213)	The Medical Expenditure Panel Survey (MEPS) - of 15,000 households under the Agency for Healthcare Research and Quality Adult population, USA (2005)	Antidepressants	Only diagnosis (indication) was considered. Scientific evidence for off-label use was categorized as strong scientific evidence or overuse.	Off-label proportion Overuse (use with limited or no scientific support)	30% of antidepressants use was for off-label indications; 96% and 28% for old and new antidepressants, respectively. 20% of antidepressants use was considered overuse; 26% and 74% for old and new antidepressants, respectively. Older age (OR = 0.95) and poor mental health (OR = 0.8) were protective factors for overuse of antidepressants. Factors not predictors of overuse: sex, ethnicity, education, income, insurance, and physical health	Misclassification was possible due to self-reported indications (undesirability of reporting mental health issues and lack of knowledge of diagnoses and treatments) Over estimation of overuse: missing diagnosis and refill administrative codes were grouped with overuse.
Ornstein *et al*., 2000 (218)	Primary care network of physicians using EHR (1996) - Incident patients with depression diagnosis or patients who were treated with antidepressant (USA)	Antidepressants	No explicit definition was used	Incidence of depression and antidepressant use	1.6% of patients were newly diagnosed with depression. 50% of incident cases were treated with antidepressants and the 46% received no medication. 40% of patients who received antidepressant had no diagnosis for depression. Diagnoses include pain (15%), headache (4.8%), sleep disorder (2%), malaise/fatigue (1.1%), obesity (1.1)	The study was designed mainly to study incidence of depression and antidepressant treatment.

The Medical Expenditure Panel Survey (MEPS)

Table 2.1 (Continued) Studies that measured off-label prescribing in adult population and primary care setting

Study	Data source and setting	Drugs included	Definition of off-label	Primary and secondary outcomes	Result	Limitation
Loder *et al.*, 2004 (215)	One speciality headache clinic affiliated with two teaching hospitals (USA) A prospective record of all prescriptions written to 379 adult patients during a 30-day period in 2003.	Drugs prescribed for headache	Only indications were considered	Prevalence of off-label use for headache	Prevalence of off-label use: 47% involving 23 drugs. 4 drugs (topiramate, lamortigine, venlafaxine, botox) accounted for more than of the off-label use. Triptans and NSAIDs accounted for two-third of the on-label use.	Limited representativeness and generalizability since patients were recruited from one speciality clinic with two practitioners.
Erickson *et al.*, 1980 (165)	A chart review of 500 drug uses in a family practice with a family medicine training site with 18 family practice residents and 9 physician faculty members, USA (1978)	All drugs were included.	Only indications were considered	Proportion of unlabeled indications Level of knowledge of physicians regarding indication noted in the FDA-approved labeling	9.2%±2.5 drug uses were for unlabeled indications. Physician knowledge of drugs: 69.3% of the indication-drug pairs were correctly identified as FDA-approved or not approved. No statistically significant difference between staff physicians and residents in correct responses to drug-indications questions.	Drugs and indications were not normally linked in patient chart and the chart reviewers needed to make the link which might have resulted in some degree of misclassification. Generalizability was limited since the study was performed in one family practice with limited number of physicians.

(similar to NDTI) and evaluated the off-label prescribing prevalence in the three top selling drugs in each of 15 drug classes as well as serious ADEs reports to the FDA due to off-label uses. The off-label prescribing prevalence estimated in 2003 was 21% overall and was higher for anticonvulsants (74%), antipsychotics (60%), antidepressants (40%), COX-2 (17%), than cholesterol lowering agents (4%) and diabetes drugs (3%). The usual culprits with highest off-label proportion include gabapentin (90%), quetiapine (78%), risperidone (65%), trazodone (56%), azithromycin (45%), and olanzapine (42%). Moreover, the authors reported on off-label use which caused serious ADEs and harm to patients. There were a total of 800 serious ADEs report filed with the FDA due to off-label use in 2002 involving 45 drugs. Since spontaneous reporting of ADEs identifies 1-10% of ADEs, this number was extrapolated to an estimate of 8000 – 80,000 serious ADEs attributable to off-label use in 2002. The report estimated that the cost of off-label prescribing would reach 12.9 billion or 30.3% of the total drug cost. This is a newspaper report with limited data on the details of the methodology of the data collection, drug, patient and physician selection as well as evaluation of off-label prescribing prevalence. However, the off-label prevalence reported is similar to Radley *et al* (18).

Several studies have evaluated the prevalence of off-label prescribing using The National Ambulatory Medical Care Survey (NAMCS). These data are collected to measure health care resource utilization in the US. NAMCS uses a multistage probability sampling design where the counties are the primary sampling units and physician practices and patient visits are the secondary and tertiary sampling units, respectively (219). Physicians participate for one week in a calendar year where they record diagnoses and treatments for sampled patients. Unlike the NDTI, the medications and the diagnoses are not linked and only face-to-face visits are included. A maximum of 3 diagnoses and 6-8 drugs are recorded per visit according to the calendar year.

A study by Lin *et al* (212) evaluated off-label prescribing prevalence and the patient determinants of beta-blocker use using 1999 – 2002 NAMCS data. Out of the 127.3 million visits with beta-blocker prescriptions, the authors found that 52% were prescribed for off-label indications where propranolol had the highest rate (59.5%) followed by metoprolol (52.9%) and atenolol (51.3%). Significant predictors of off-label prescribing included older

age, male patient and increased number of drugs and visits to specialists than visits to general practitioners. Due to the restriction on the number of diagnoses and the number of drugs that can be recorded on patients visit, the studies are generally susceptible to misclassification biases. First, if there is a mismatch between the recorded drugs and diagnoses, it is impossible to know whether the diagnosis is not recorded due to the restriction or the diagnosis is not part of the patient's problem list. Second, the absence of a link between the drug and the diagnoses made the determination of on-label and off-label even more difficult.

Sugarman *et al* (211) evaluated off-label prescribing of drugs for the ten most common dermatologic conditions for which medications are indicated using the 1990 – 1997 NAMCS data of. Off-label prevalence was 32% with a range from 17% to 73%. Non-dermatologists prescribed more off-label drugs for dermatologic conditions than dermatologists. The highest prevalence of off-label prescribing was reported for acne rosacea (73%) and actinic keratosis (52%). The most common drugs prescribed for an off-label indication include tetracycline and erythromycin. The lowest off-label use was noted for conditions where many approved drugs exist for these indications including atopic dermatitis and psoriasis.

Lai *et al* (210) evaluated the off-label use of antidepressants for insomnia using the 2006 NAMCS data where they reported 45.1% of insomnia was treated with antidepressants. The authors used Eisenberg's theoretical framework to select potential determinants of off-label use including patient and physician characteristics and physician office settings. However, the methods used to identify insomnia patients and assignment of on- and off-label status had serious limitations. The authors used a three-step process to identify on- and off-label insomnia treatments. First, visits where at least one 'frequently used insomnia drug' was prescribed were considered potential insomnia treatments. Neither patient diagnosis nor treatment indication was considered. Second, all drugs approved to treat insomnia (benzodiazepines and drugs related to the benzodiazepines) were considered as on-label, even though they may have been prescribed for other "off-label" indications. Third, the five antidepressant drugs identified as 'frequently used for insomnia' were considered off-label treatment for insomnia after patients with depressions were excluded. The first step did not help to assemble patients with insomnia; it created group of patients who received the specified drugs since the drugs could be prescribed for other conditions as well. Considering

all treatments with benzodiazepine or the related drugs as on-label without diagnosis of insomnia might have inflated the on-label use proportion of these drugs. For example, in another study, 40.7% of one of the study drugs (Zolpidem) that was classified as on-label insomnia treatment was used to treat off-label conditions (33). The third step which created the off-label use of antidepressants for insomnia assumed that if an antidepressant was not prescribed for depression, it must be for insomnia. However, antidepressants have numerous other on- and off-label indications other than insomnia and depression. As a result, the findings of this study are impossible to interpret.

Pearce *et al* (209) evaluated off-label prescribing and trends of prescribing of calcipotriene using 1991 – 2001 NAMCS data. Among the 5.8 million calcipotriene mentions, the off-label prescribing prevalence was 57%. Two distinct trends in use were observed; a rapid rise in the prescribing of calcipotriene immediately after the drug's approval in 1994 and a rapid decline in 1998. The rapid rise and fall was primarily attributed to off-label use by non-dermatologist physicians, and by female and white patients. As all the other studies that have been conducted using NAMCS data, the off-label prevalence of 57% may be inflated by the restriction in the number of diagnoses (n=3) that could be recorded relative to the number of drugs (n=8). This inflates the off-label prevalence since unrecorded or incorrectly coded on-label indications were grouped as off-label indications. Even though calcipotriene is never been used for vulvovaginitis, it was the second most prevalent diagnoses associated with the drug. Miscoding was apparent since vulvovaginitis (ICD-9 code: 616.1) and psoriasis, the approved indication, (ICD-9 code: 696.1) have identical coding except the second digit. The finding where non-dermatologists prescribed more off-label than dermatologist could be explained with the misclassification of psoriasis diagnosis. Since dermatologists deal with a restricted repertoire of ICD-9 codes, they are less likely to incorrectly code for psoriasis compared to non-dermatologists who were exposed to dermatologic patients occasionally (e.g. other specialties) or physicians who deal with diverse patient population and diverse ICD-9 codes (e.g. general practitioners). This study underlines the need for validation studies before embarking on the use of any data collected primarily for other purposes.

The next two studies used US Medicaid data to evaluate the prevalence of off-label prescribing in specific classes of drugs. Chen *et al* (81) in 2005 had evaluated off-label

anticonvulsant use in Georgia Medicaid patients, quantified evidence-based off-label uses and identified determinants of off-label anticonvulsant use. The study used a 2-year window to identify anticonvulsant drugs and all ICD-9 classified diagnoses. Off-label use was defined as: 1) a non-approved (off-label) treatment indication, 2) age group excluded from approved use, or 3) drugs approved only as adjuvants, not primary therapy. To quantify off-label use indications, all ICD-9 codes from a patient's computerized medical claims were mapped to ICD-9 coded translations of the approved on-label indications of each anticonvulsant. The prevalence of off-label anticonvulsant prescribing was 71.3% and in the majority (96%) of these off-label uses, the indication criterion of off-label assignment was not fulfilled. From 19% to 57% of the off-label uses were not supported by evidence from RCT or Cochrane review. Higher prevalence of off-label prescribing was observed for anticonvulsants marketed after 1993. Gabapentin (86%), lorazepam (80.3%) and diazepam (72.7%) had the highest off-label prevalence. Important predicators of off-label use included older age, females, non-whites and patients with depression, pain or epilepsy, and having a neurologist as a prescriber. The study also demonstrated the non-specificity of the ICD-9 codes as a tool to capture treatment indications. The use of general (three digits ICD-9) and specific (more than three digits) resulted in a sizable difference in the percentage of evidence-based off-label use. In addition, the lack of direct or temporal link between drug and indication might have led to underestimation of the off-label use since a drug could be considered a treatment for a diagnosis even if the two appear two years apart or the drug preceded the diagnoses. For example, for a patient treated with tiagabine (an anticonvulsant) for chronic back pain (off-label indication) and who later developed seizure as ADE of the drug, tiagabine and seizure will be paired together and the treatment will be considered on-label. Overestimation of off-label use was also a possibility due to miscoding of approved indications or failure to code the treatment indication properly.

The second study (214) also used Georgia Medicaid data, for years 2000 – 2001 and investigated off-label use in antidepressant, anticonvulsant and antipsychotic adult recipients. The criterion for off-label use included only indication i.e. whether the 'indication' was recorded in claim for specific drug. The authors reported off-label prescribing of 80.1% for anticonvulsants and 63.6% and 75.4% for antipsychotics and antidepressants, respectively. Off-label prescribing for specific drugs includes amitriptyline (81.3%), paroxetine (66.9%),

trazodone (65.6%), gabapentin (98.0%), lorazepam (88.6%), risperidone (66.8%), quetiapine (59.3%) and olanzapine (51.7%). Significant determinants of off-label use include >65 years of age, white race, drug age (new anticonvulsant), specialty of the physician, and some comorbid conditions (renal failure, major depression, mental retardation, Alzheimer's disease, neurologic disorder, psychosis, schizophrenia and pain problems). The authors identified coding problems (over/under coding, coding errors, missing codes) and lack of direct link between diagnosis codes and prescribed drugs as limitations of the study that would influence the prevalence of off-label prescribing.

The next three studies from Europe (two The Netherlands, one Austria) included in the review used a variety of methods to evaluate off-label use. Gijsen *et al* (205) studied ill-founded off-label prescribing in the Netherlands using the "Netherlands Information Network of General Practice". Ill-founded off-label use was defined as "an off-label use where there is no support in pharmacotherapeutic handbooks or clinical practice guidelines". Among the 48 ill-founded off-label uses, 21 did not occur in Dutch general practice (comprised of 78 general practices and 319,843 patients). Drugs and diagnoses were recorded in electronic medical records and diagnoses were coded by International Classification of Primary Care (ICPC-1) codes and drugs by ATC-classification. The prevalence of ill-founded off-label use was 0.9%, which is very low compared to other studies (18) and this is because only a small percentage of drug-off-label use combinations which lacked scientific evidence for their use were selected for evaluation. The highest proportion of ill-founded off-label prescription was reported for betahistine (26.7%). The four leading drugs and indication pairs with ill-founded off-label use were betahistine (dizziness), etoricoxib and celecoxib (back pain), and amitriptyline (headache). Potential information bias may have contributed to an underestimation of prevalence since more than a quarter of the prescriptions (27.6%) had no ICPC-1 (diagnosis) code and this might have resulted in underestimation of off-label use if lack of code was associated with off-label indication. In addition, there is no direct or temporal link between drug and indication and the treatment indications were not validated.

Rijcken *et al* (216) investigated antipsychotic drug use in family doctors practice involving four general practitioners and 192 patients in northern Netherland. The methodology involved retrieval of prescriptions from the pharmacy. Information on the diagnosis,

diagnosing physician and prescriber was obtained from the treating physician using a questionnaire. Drug data from the Dutch Medication Evaluation board was used to assign drug-indication approval status. The authors reported on off-label use of antipsychotic drugs and quasi-label (off-label indication with psychosis as an inherent comorbidity) stratified by sex. Males were over-represented in the quasi-label group while females were over-represented in the on-label group. Off-label use between male and female were comparable. Generalizability of results was limited due to small sample size of patients and involvement of only one practice.

Weiss *et al* (217) investigated off-label prescribing in patients who had their antipsychotic drug filled at local pharmacies in 1996 – 1997. The authors reported 66.5% off-label use. A pharmacy student retrieved information on treatment indication from patients through telephone interview. More than half of the patients described the treatment indications for the antipsychotics as 'tranquilizer' or 'anxiolytic'. In addition, classical indications (schizophrenia-related and bipolar affective disorders) were common in married or widowed patients than unmarried or divorced patients. Patients with classical indications suffered more side effects than non-classical indications. The main criticism of this study involves the source of treatment indication information. Patients might not supply the correct treatment indication especially for drugs like antipsychotics. Using ICD-9 codes has a number of issues when it is used to identify treatment indications and using patients own terminology and mapping to treatment indication is a daunting task and might led to differential misclassification bias.

Conti *et al* (213) investigated antidepressant off-label prescribing and overuse (off-label with no strong scientific evidence) using the Medical Expenditure Panel Survey (MEPS) of 15,000 households representing the adult United States population in 2005. The authors reported a 30% off-label use of antidepressants; 96% and 28% for old and new antidepressants, respectively. Two-thirds of off-label use (20%) had no strong scientific evidence (defined by the authors as over-use); 26% and 74% for old and new antidepressants, respectively. Older age (OR = 0.95 per year) and poor mental health (OR = 0.8; yes vs. no) were protective factors for overuse of antidepressants. Sex, ethnicity, education, income, insurance, and physical health were not predictors of overuse of antidepressants. The survey methods of

this study are completely different from the two surveys (NDTI, NAMCS) described previously. This survey has been conducted since 1996 and has two components: self-reported antidepressant treatment in the household and prescription drug. During a face-to-face interview, medical events including diagnoses and drug treatments were abstracted from calendars and diaries of survey participants. In addition, the survey staff contacted medical providers to validate the medical visits including drug names and the conditions associated with each medication. There are a number of methodological issues on the use of such data to evaluate off-label prescribing. A validation study (220) that compared patient-reported data with data from the medical providers found an overall sensitivity of 74% when all medical conditions were categorized into 23 broad groups. The specific sensitivities for categories included 37% (anemia), 87.7% (mental health and substance abuse) and 93% (pregnancy). The sensitivities were lower for subcategories of medical conditions. The validation study showed that such a data is desirable to estimate prevalence of major health conditions and associated cost in the population for certain categories of health problems however the use of such data to document treatment indication is likely insufficient to provide the needed precision of therapeutic intent. Even ICD-9 codes lack the precision needed to document treatment indications for many conditions. Since drugs are approved for specific treatment indications, evaluation of drug use as on- or off-label needs data which points to specific treatment indications. In addition, reporting bias of drug and indication was possible since they were self-reported (undesirability of reporting mental health issues and lack of knowledge of diagnoses and treatments). Another source of misclassification could result when indications obtained from patients were linked to ICD-9 codes. The authors grouped all problems with no diagnosis to off-label which lacked scientific evidence and this might have led to an over-estimation of overuse since lack of diagnosis does not mean off-label use.

Ornstein *et al* (218) evaluated pharmacologic management and follow-up of newly diagnosed depression patients and patients who were prescribed antidepressants without a depression diagnosis in primary care practice using an electronic health record. While the study did not specifically address off-label use, the result could be used to estimate the off-label use. The incidence of depression in 1996 was 1.6%, and half of the patients subsequently had received antidepressant drugs. At the same time, 1.4% patients were newly treated with antidepressant

drugs without a diagnosis of depression, which results in a prevalence of 46.6% of off-label use of antidepressants. Non-headache pain and headache accounted for 20% of the off-label indications. The off-label prevalence might be overestimated since lack of depression diagnosis in an EHR does not translate into patient not having depression. There is a need to validate the diagnoses entered in EHRs with another gold standard to measure the extent of misclassification of depression.

Erikson *et al* (165) evaluated off-label prevalence in 500 drugs used in a family practice and training site comprising 18 family practice residents and 9 physician faculty members in the United States (1978). This is the only study that measured off-label use and surveyed physicians on their knowledge of drugs and treatment indications. The authors reported 9.2% off-label use and dipyridamole was the most frequent off-label drug. Seven out of 10 physicians from a sample of 91 physicians correctly identified the FDA-approval status of drug-indication pair and there was no statistically significant difference between residents and faculty in knowledge of drugs. Generalizability of results is limited since only one practice was used to evaluate off-label use and only 55% of physicians participated in the survey.

Loder *et al* (215) evaluated off-label prescribing in one specialty headache clinic that was affiliated with two teaching hospitals in United States. Prospective records of all prescriptions written to 379 adult patients during a 30-day period in 2003 were included in the study. Forty-seven percent of the drugs were used off-label; where new anticonvulsants (topiramate, lamortigine) and new antidepressant (venlafaxine) accounted for 15% each. Among the on-label drugs, triptans accounted for 37% and non-steroidal anti-inflammatory drugs for 32%. Potential bias might have been introduced since prescribing physicians were also tasked in the evaluation of FDA-approval status. Generalizability is also limited since the study was on one specialty clinic affiliated with teaching.

Off-label use and adverse drug events

Phase III RCTs are designed to address efficacy and to identify common ADEs in association with the study drug's specified treatment indication(s). Rare ADEs and ADEs which occur with long term use of drugs are identified with large scale RCTs and post-marketing surveillance methods. Information on the efficacy and safety of the drug in relation to the off-label indication is generally not available for newly approved drugs but there might be some safety and effectiveness data for 'older' drugs. As a result, off-label prescribing is potentially dangerous. As few drugs are tested in children, most of the literature on the association between off-label use and adverse effects is generated by studies in pediatric populations (21-25).

In contrast, there is little systematic investigation in adult populations of the association between off-label use and ADEs. Unlike the pediatric population, and where off-label use is defined by ages excluded from RCTs, in adults, off-label use is typically defined by treatment indication—indications for which the drug was not approved. The lack of systematic documentation of treatment indications in practice has severely curtailed comprehensive investigation of the prevalence and outcomes of off-label use. Studies which investigated off-label prescribing were based on physician surveys and administrative health data which do not have a follow-up data on patient outcomes which can inform on the occurrence of ADEs. In children, the main criterion used to determine off-label use was whether the drug is approved for specific age group. Since age is readily available, the determination of off-label use is relatively easy. Thus most of the studies in adults on the association between off-label use and ADE are based on case reports or case series that are notable because of the high rate of mortality and morbidity.

Fenfluramine-Phentermine (Fen-Phen)

The deleterious effect of off-label use of fen-phen was shown in a number of studies (28;221-226). Fenfluramine (the fen- part of fen-phen) was approved in 1973 in the US to treat obesity. The drug manufacturer, A.H. Robbins, received a "disapproval letter", from the now famous FDA employee Dr. Robert O. Knox, citing that 'the drug was not shown to affect the course of obesity over long term'. However, this FDA decision was repealed and

Dr. Knox was transferred in response to A.H. Robbins' objections to the letter. Fenfluramine was finally approved as *single drug, short term use for obesity*. The transfer of Dr. Knox was investigated by a United States congressional body, and FDA officials involved were reprimanded (223). The Phen- part of fen-phen, Phentermine, is an amphetamine-like stimulant approved in 1959 as a weight loss drug.

Limited efficacy of Fenfluramine and phentermine led to lagging sales in the 1970s and 1980s. In addition, fenfluramine was known to produce numerous neuropsychiatric side effects including drowsiness, altered mood, and memory loss. As a result, most people did not stay on the drug for a long time. Phentermine also has common side effects such as palpitation and insomnia. In 1979, Dr. Michael Weintraub came up with the idea of combining the two drugs to counteract the side effects of one another so that patients could stay on the drugs long enough to produce an effect on their weight. Through official NIH funding and unofficial A.H. Robbins support, 121 obese patients with mean weight of 200 pounds were randomized to evaluate the combined effect of the two drugs. Patients on fen-phen lost 30 pounds when combined with diet restriction, exercise and behavior modification. Thirteen patients (10.7%) dropped out from the study due to ADE including four related to unspecified cardiovascular events. While the study was completed in 1987, the article was published much later in 1992 as a journal supplement (227), supported by an undisclosed pharmaceutical company at the time when obesity was recognized as a chronic disease in the medical community including the Institute of Medicine and National Health Institute (228;229). Soon after publication, reprints of the article widely circulated to doctors' offices. In 1995, the article received mainstream media attention after it was covered by *Allure* magazine and later by *Reader's Digest*. Physicians prescribed fen-phen, a combination drug that was not approved by the FDA, for everybody who asked for it whether obese or not using a variety of venues (223). As a result, 18 million fen-phen prescriptions were dispensed in a month in 1996 (230). While fenfluramine was known to cause primary pulmonary hypertension in Europe, only four cases were reported in the USA. A cardiac sonographer, Pam Ruff, postulated the link between fen-phen and cardiac valve damage after noticing the unusual occurrence of valve damage in younger female patients sent for echocardiography. She had collected data for 2 years before contacting Mayo clinic. Physicians in Mayo clinic had noticed this association in some of their patients. By

combining the two centers patients, a case series was published on *NEJM* linking fen-phen to heart valve damage (28). The FDA received 75 reports of heart valve damage and use of fen-phen after the *NEJM* publication. As a result, FDA initiated a study (221) in five centers on users of fen-phen or dexfen-phen (an isomer of fenfluramine approved in 1996 for obesity treatment). The prevalence of valve abnormality in users of these drugs was 33% (range: 30%-38%). Based on these data, the manufacturers were forced to withdraw fenfluramine and dexfenfluramine from the market on September 15, 1997. The association between the drugs to heart valve damage was replicated in numerous studies, however the incident rate reported was lower (222-226).

Hormone replacement therapy (HRT)

Over three-quarters of a century hormone replacement therapy has been used to reduce the effects of aging and treat a myriad of medical conditions (231). The presumed benefit of HRT led to off-label prescription of these drugs for peri-menopausal, menopausal and well post-menopausal women for primary and secondary prevention of heart disease, prevention and treatment of cognitive decline, and dementia. As a result more than one-third of women aged 50 to 74 years were placed on HRT in 1995 (232). However, the approved product label of Premarin and other HRT-related drugs included only the relief of menopausal and postmenopausal symptoms including vulvar and vaginal atrophy and prevention of osteoporosis. In response to a broadening of marketed treatment indications, the FDA was forced to write a warning letter to the company Wyeth-Ayerst on the promotion of the drug to "broad and ambiguous health claims for Premarin that promise yet-to-be substantiated or even identified health benefits from the use of Premarin" (233). Although Premarin was known to increase the risk of endometrial cancer since 1970 (234), the risk and benefit of HRT for other marketed indications was not investigated in RCT prior to the 90s'. A number of RCTs were undertaken in the late 1990s which clearly showed that HRT increased the risk of coronary heart disease, invasive breast cancer, stroke, and dementia without benefit to cognitive functioning or health related quality of life (30;235-239). The story of HRT illustrated the value of RCTs, as well as the potential deleterious effects of off-label use.

Quinine

Quinine is a drug approved to treat plasmodium falciparum malaria and is one of the legacy drugs that were approved before the 1960s when limited information on the safety, effectiveness, and quality of production of drugs was needed. The drug has a number of known ADEs including cinchonism, QT prolongation, change in heart rhythm, thrombocytopenia, permanent hearing and visual disturbance, renal failure and generalized anaphylaxis. The drug has been used off-label to treat nocturnal leg pain since the 1940 (240). In Canada, according to the Canada adverse drug reaction newsletter, there were 71 serious ADE reports suspected with quinine use. More than half of all reported events were life threatening or required hospitalization (29). Only four reported that the treatment indication was for malaria. Reported ADEs include severe thrombocytopenia, Stevens-Johnson syndrome, vasculitis and arrhythmia. In the US (241), there were 665 ADE reports for quinine between 1969 and 2005 and 38 between 2006 and 2008, respectively, including 98 reported deaths. Out of the 38 reports, only one was for malaria. As a result of these reports, both the USA (241) and Australia (242) declared the lack of justification to treat nocturnal leg pain with quinine due to the risk of the severe ADEs. The US FDA released a safety communication letter directed to physicians and patients in 2010 (243). In addition, the American Neurology Society confirmed that, based on their synthesis of the available literature, they did not recommend quinine for routine nocturnal leg pain (244).

Tiagabine

Tiagabine is approved as adjunct therapy to treat seizure disorders. The drug company, Cephalon, engaged in off-label marketing of the product using various venues (141). As a result, tiagabine was increasingly used off-label to treat psychiatric and pain conditions including bipolar disorder, anxiety and neuropathic pain (245). In 2006, the FDA sent a letter to warn physicians about ADEs including new onset of seizure and status epilepticus in patients without epilepsy, and added a black-box warning to the label (31). Most troubling was the practice of treating physicians to increase the dose of tiagabine in the hope of controlling the newly developed seizure without realizing that tiagabine may be the causative agent of these new symptoms. Concomitant drugs or an increase in the usual dose of the drug were postulated to contribute to the onset of seizures by decreasing the seizure threshold (27;245). In addition, tiagabine had another FDA warning concerning the risk of suicidal behavior and suicidal ideation (246). The company pleaded guilty to illegally

promoting (promotion of drugs for uses not approved by the US FDA) three of its drugs, including tiagabine, and agreed to pay 425 million dollars (247).

Monitoring off-label uses and their effects

Currently, there is no concerted effort by drug regulatory bodies to actively investigate the association between off-label uses and adverse outcomes other than the co-ordination of voluntary reporting of adverse drug events. As it was demonstrated with the aforementioned examples, associations between off-label use and adverse outcomes were discovered either because it was a popular drug and a rare outcome (e.g. fen-phen and valvular heart damage) or the paradoxical nature of the drug's association with the outcome (e.g. tiagabine and seizure). In the case of quinine, the only approved indication is for malaria, a condition that is rare in the US or Canada and most of the users of the drug are older individuals. When the adverse outcome is common and the drug use is widespread, it is difficult to identify the adverse events that are potentially related to drug exposure. The case of hormone replacement therapy is a classic example. Approximately one-third of peri- and menopausal women used these drugs for various conditions, many of which were likely for off-label indications. The adverse outcomes later identified to be caused by the drugs such as breast cancer, coronary heart disease and dementia are also quite common, which leads to the failure of ADE reports to discover them. Only large scale RCTs were able to unearth the association between these drugs and their adverse outcomes.

Nowadays, meta-analyses of RCTs where the treatment indications are unambiguously spelled out are increasingly used to investigate the effectiveness and safety of drugs for off-label indications. Systematic reviews of the off-label drugs and their uses have been advocated by some authorities in the field of off-label prescribing, suggesting that priority be given for: 1) off-label uses with questionable scientific evidence, 2) where there have been black box warnings for the particular indications, or 3) which are costly (33). Examples of this approach and others to evidence generation are outlined subsequently.

Atypical antipsychotics

Atypical antipsychotics are increasingly used to treat off-label conditions (208) even though they carry a black box warning that identifies serious adverse events (248) after increased risk of death was identified in elderly dementia patients (249;250). Later, systematic reviews (247;251) investigated the efficacy and comparative effectiveness of these drugs for off-label uses by evaluating more than 12,000 citations and 162 studies. The review identified small statistically significant favorable outcomes for psychosis, mood alteration and aggression in dementia patients for aripiprazole, olanzapine and risperidone. Adverse events reported in the elderly include risk of death, stroke, extrapyramidal symptoms and urinary tract symptoms with number needed to harm (NNH) ranging from 10 for extrapyramidal symptoms to 87 for death. Short of publication bias and suppression of unfavorable findings, meta-analyses are best suited to evaluate effectiveness of drugs for off-label indications.

Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa), a drug approved as an orphan drug to treat bleeding in patients with hemophilia with inhibitors to factor VIII or IX at a cost of 10,000 dollars per dose, was used more than 95% of the time for off-label indications to prevent and to treat other bleeding conditions (252). The company illegally promoted the drug to health professionals as a coagulation agent for a variety of off-label uses including post-trauma, surgery, transplant and intra-cerebral bleeding, and eventually paid $25 million for illegal promotion in the US (253). These off-label uses were also discussed in a symposium organized by the company in 1999 (254). Recent systematic reviews showed that the drug did not reduce mortality and increased thromboembolic events (255;256). The debate between clinicians favoring systematic reviews and RCT's and clinicians favoring experience is ongoing (257-259).

Role of observational studies in off-label use monitoring in real-world settings

Clinical trials have limitations in addressing ADE questions related to on-label and off-label uses. Moreover, most off-label uses lack published clinical trials altogether. Observational studies based on drug utilization databases may fill this gap however they lack the treatment indication for the drug use (26). Recently, new methods have been identified that try to measure treatment experiences directly from patients. PatientsLikeMe is a web-based community and research platform where more than 150,000 patients share their treatment

experiences including symptoms, disease conditions (more than 1000), drugs (prescription, over-the-counter, supplements), treatment modalities (physical therapy, psychotherapy, life style modification) and their treatment outcomes (260-262). The data entered by patients was used to evaluate off-label prescribing of modafinil and amitriptyline across five condition-based communities including multiple sclerosis, fibromyalgia/chronic fatigue syndrome, ALS, mood disorder (depression, bipolar and anxiety disorders). Patients reported treatment histories including the purpose for taking the medication, side effects and perceived effectiveness. For modafinil, 98.1% (1721/1755) of its use was for off-label indications including general fatigue (68%), excessive daytime sleepiness (16%), and difficulty concentrating (3%). Moderate to major effectiveness ratings were given by 72% of the patients and it was reported that the effectiveness did not vary by treatment indication. The three most frequently reported side effects were jittery feeling (18%), dry mouth (16%) and anxiety (12%). For amitriptyline, the off-label use was 91% which included insomnia/other sleep problems (27%) and pain (17%). Excess saliva was the purpose of treatment for 40% of ALS patients. The side-effects reported include sleepiness, dry mouth, and weight gain. Higher effectiveness was reported for the off-label indications than the on-label indication (52% vs. 40%). PatientsLikeMe presented a novel approach of capturing patient outcomes using patients as the primary source; information that can supplement other sources of data. However, further research is needed to create validation mechanisms of ascertaining entered data and claimed diagnosis, treatment and the existence of patients.

Web-based intensive monitoring (Netherlands) is another patient-based new method which documents treatment indication and drug outcome data (263). Eligible patients are identified in the pharmacy when filling an incident prescription for a study drug. Patients are informed about the study and information was given to register online. The registration includes documentation of demographic (age, sex, weight, height) and drug related information (start date, dosage, treatment indication and concomitant medications). Periodically e-mails are sent to patients to probe on the occurrence of possible ADEs, its seriousness, and its outcome and whether there is any drug therapy change (stopping or dose reduction). This method was applied for the study of pregabalin (264) and duloxetine (265) and it was successful in capturing treatment indications and ADEs. However, the response rate of

patients were very low, 6.6% and 3.5% for pregabalin and duloxetine, respectively and no information was available to evaluate the non-responders.

Risk factors for adverse drug events

While observational studies can complement RCTs in drug safety studies, non-random allocation of treatment to patients creates confounding by indication – a bias due to "a collection of less explicit characteristics of both the patient and the prescriber that influences the choice of a particular drug for a particular patient at a particular time" (266). As a result, important determinants that increase the risk of ADE need to be identified and incorporated in observational studies. Table 2.2 shows the review of studies related to ADEs from 1960 to recent days. Few studies examined the association between off-label use and ADEs. While the early studies examined from one to few risk factors at a time, the later ones included more risk factors. However, only few studies included all important risk factors in multivariate regression models. There is also great variation in how ADEs are ascertained by health care setting.

Old age has been identified as one of risk factor for ADE in a number of studies (267-274). However, whether aging per se is an independent risk factor or whether it is simply an individual characteristic that is strongly correlated with the probability of having more medical problems and more drugs, both of which increase the risk of ADE (275). Studies which accounted for number of drugs the patient was taking did report attenuation of the age effect (276;277) or the disappearance of age effect altogether (272;274;278-285). All studies show that number of drugs is an independent risk factor for ADE. Comorbidity is also the other factor closely related to age and number of drugs. Various studies showed the independent contribution of a number of comorbidities in the development of ADE (277;278;286-290). However, others showed the lack of association (282;283;291) and these discrepancies might be related to inclusion of other important risk factors.

The sexes have different pharmacodynamics and pharmacokinetics profiles (292), respond differently to certain drugs (293) and vary in visits to medical establishments (294-296), all of which may lead to variable rates of development and detection of ADE. Higher rates of

ADE were reported for females (267;279;281;285;297) but other studies found no association between sex and ADE (269;282;283;291). None of these studies accounted for the frequency of visits or the continuity of care that the patients received from their physician which may influence the detection of ADE. Two systematic reviews (298;299) have shown the beneficial effect of increased continuity of care which include decreased hospitalization (300-302), decreased length of hospital stays (300), increased immunizations (303) and decrease in readmission rates (304). These favorable outcomes may be mediated by earlier identification of patient needs and problems and the institution of appropriate management.

The type of drugs also plays a role in the probability of ADE. Research has shown that Central nervous system, cardiovascular and anti-infectives were more often implicated with ADEs (273;278;291;305). Another drug characteristic that led to differential reporting of ADEs was the age of the drug; new drugs to the market generate more spontaneous reporting of ADEs (306;307). However, the classic Weber effect where increase in reports of ADE in the first two years and decline thereafter in spite of the progressive increase in prescribing rate of the drug is not consistently shown (308;309).

Table 2.2 Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Results	Limitation
Martin *et al.*, 1998 (267)	- All prescription event monitoring studies from 1982 - 1997 (47 national cohort studies) - Primary care setting in the UK - 513,608 patients (UK)	·47 new drugs	Incidence of suspected ADR by sex and age categories. Method was described in PEM.	Suspected ADR: events the prescribing physician indicated as suspected ADR. Sex Age	Incidence of suspected ADR: 16.9 per 10 000 patient-months of drug exposure Incidences: - males: 12.9 per 10 000 - females: 20.6 per 1000 - RR = 1.6 (1.5, 1.7). Highest rates: females (30-39 yrs) and males (50-59 yrs) No clear association between age and reporting of ADR.	Response rate for the green form was 56% with range from 42%- 68%. 10% of physicians who produced 42% of the prescriptions belonged to the low responders and are poorer prescribers and perform poorly in patient follow-up. There might be more ADR in their patients' population → underestimation of ADR. The incidences were not adjusted for number of visits. Females generally have more visits which may lead to more opportunity to detect ADRs.
Frost *et al.*, 2010 (129)	PatientsLikeMe:a web-based community of patients where patients record their disease and treatment experiences 1316 patients: multiple sclerosis, Parkinson and mood disorders 1394 patients: ALS, depression, sleep disorder,	Modafinil and amitriptyline	Side effects and effectiveness reported by patients	Off-label prevalence, side effects and self-reported effectiveness. Off-label status was considered as a determinant.	98% and 91% off-label use for Modafinil and amitriptyline, respectively. 40% of amitriptyline was used to control excessive salivation in Amyotrophic Lateral Sclerosis. No variation in effectiveness by indication (Modafinil) Effectiveness was better for off-label indications than on-label indication. (Amitriptyline)	Verifying the patients' existence and their experience is presently difficult. Members may not be representative of the patients with the conditions. Measures of effectiveness and side effects were simplistic and there is no mechanism of evaluating the claims of effectiveness or vice versa.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Jonille-Bera *et al.*, 2005 (24)	Physicians report of serious or unexpected ADRs to their 31 Regional Pharmacovigilance Centers in 5-month period. 182 adult and children with ADR (France)	No drug was excluded	ADR were defined according to the French method (very probable, probable, possible and doubtful)	Percentage of ADR in incorrectly used vs. correctly used Correctly (incorrectly) used depend on the label of the drug and include indication, contraindication, dose, route of administration, frequency, and interaction with other drugs. Off-label status was considered as a determinant.	- 182 ADR reported in 5-months - Incorrect use: 26% of drugs. - indication not licensed – 7.3% - drug interactions – 10% - incorrect dosage – 5% - inappropriate duration – 3.1% - contraindications – 0.9% - Proportion of drugs with ADR: - ≥ 1 drug label criteria not followed vs. all criteria followed: 76%, 59.4%; p = 0.0001 - indication not licensed vs. licensed: 79%, 62%; p<0.02	Small sample size with mixed population (children and adult) Terminologies used (correctly, incorrectly) are confusing. The term 'off-label' might be used with small modification rather than creating a new term with little universal appeal.
Maher *et al.*, 2011 (251)	Studies of atypical antipsychotic medications on off-label indications till May 2011. - RCTs for adult off-label conditions. - Observational studies with sample sizes of > 1000 patients. -- 2066 articles underwent full text review. - Result generated from: 162 trials with efficacy outcomes and 231 trials or large observational studies with adverse event reports.	Atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone)	Adverse events reported in publications were aggregated for elderly and non-elderly	- efficacy - comparative efficacy - adverse event - comparative harm - The drugs' efficacy and adverse drug event profile were evaluated for off-label indications.	- 14 placebo-controlled trials of elderly patients with dementia: statistically significant effects sizes from 0.12 to 0.20 (aripiprazole, olanzapine, and risperidone) - 3 trials for generalized anxiety disorder: a 26% greater likelihood of a favorable response (quetiapine). - For obsessive-compulsive disorder: 3.9-fold greater likelihood of a favorable response (risperidone) - Elderly patients: increased risk of death, stroke, extrapyramidal and urinary tract symptoms. - Risk of ADE for Risperidone (pooled ORs): - Cardiovascular event: 2.10 - Cerebrovascular event: 3.12 - Extrapyramidal: 3.00	The incentive not to publish is greater for off-label indications with unfavourable outcomes since RCTs were mainly performed by pharmaceutical companies especially when the drugs are relatively new.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Levi *et al.*, 2010 (268)	35 RCT (involving 26 studies in patients and 9 in healthy volunteers)	Recombinant activated factor VII (rFVIIa)	Thromboembolic events were identified prospectively in enrolled patients and healthy controls. All thrombotic events were confirmed by objective means. Cases which were not thrombotic were excluded.	Thromboembolic events stratified by type of bleeding, - The drug uses were for off-label indications including central nervous system bleeding (31.3%), advanced liver disease (27.8%), or trauma (18.7%)	rFVIIa vs placebo: - rate of thromboembolic event, 10.2% and 8.7%, [OR = 1.17(0.94, 1.47]; - rate of arterial thromboembolic event, 5.5% and 3.2%, [OR = 1.68(1.20, 2.36] - rate of coronary arterial thromboembolism, 2.9% and 1.1%, [OR = 2.39(1.39, 4.09] Age ≥65 years vs. <18 years - rate of arterial thromboembolic event, 9.0% and 3.8%, [OR = 2.43(1.34, 4.41]	Publication bias is possible.
Hurwitz *et al.*, 1969 (272)	Belfast hospital; 1160 hospitalized patients - prospective design	All drugs were included.	- ADRs were identified through daily consultation with staff, reasons for drug therapy change, unusual course of disease and patient interview.	- ADR and four variants: sex, age, length of hospital stay, number of drugs	- Age: rate of ADR [below 60 years/60+ years: 6.3% vs. 15.4%] - Sex: rate of ADR [Female/Male: 14.2 % vs. 7.3%] - hospital stay more than 22 days: [cases/non-cases: 53.4% vs. 28.8%] - 6+ drugs: [cases/non-cases: 81.4% vs. 37.2%] - History of previous reaction: [cases/non-cases: 22.9% vs. 6.7%] - Patients with a reaction had more drugs up to the time of the reaction than would be expected in patients who did not have reactions.	Preferential recall of past events (recall bias) might have played a role in the relationship between past ADR and present ADR. Stratified or multivariate analysis was not performed to evaluate the independent contributions of number of drugs and age of patient.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Hurwitz *et al.*, 1969 (310)	Admission to Belfast hospital because of ADR; - 1268 hospitalized patients	All drugs were included.	- ADRs were identified through daily consultation with staff, reasons for drug therapy change, unusual course of disease and patient interview.	- ADR and self-poisoning	- Rate of ADR = 2.9% - Rate of poisoning = 2.1% - Median age of ADR patients: 60 years - Median age of poisoning patients: 27 years	The sample size was too small to comment on general trends and risk factors.
Pouyanne *et al.*, 2000 (311)	Representative sample of medical departments in French teaching and general hospitals - 3137 patients admitted to 62 hospital in 2 weeks period	- No drug was excluded.	- Clinicians and pharmacologist assess each patient for the occurrence of ADR and validation was performed by an independent committee.	- ADR	- ADR was the reason for admission in 3.2%; 95% CI (2.4%, 4.0% of the patients. - More female and older patient with ADR - Incidence of ADR increased with age.	No multivariate analysis where number of drug was included.
Hutchinson *et al.*, 1986 (278)	Prospective design in Internal medicine unit in royal Victoria hospital, Montreal - 1026 patients	No exclusion criteria on drugs	- ADR was identified through telephone interview at the 2nd day, 2nd week, and 1, 3 and 6 months post-enrollment. - A validated algorithm was used to assess ADRs for causality.	- ADR - age - sex - Socioeconomic status - number of drugs - history of ADR - number of active medical problems - use of tobacco and alcohol	- ADR: Suspected ADR - 292 - Possible, 66%; Probable, 19%; definite, 1% - The rate of possible to definite ADR per patient and per drug course: 16% and 7% - The rate of probable to definite ADR per patient and per drug course: 5% and 2% - ADR rate in incidence and prevalent drugs: 3% vs. 1%. - More drugs, older age, more medical problems, non-smokers increased the risk of ADR. - CNS, cardiovascular and diuretics had the highest ADR.	Multivariate analysis would be ideal to untangle the effect of age, number of medical problems and number of drugs.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Smith *et al.*, 1966 (284)	Prospective design in a hospital (one year) - 900 patients (USA)	No exclusion criteria on drugs and patients	- Physicians and nurses were questioned every day for the occurrence of an ADR in the previous 24 hours. - ADR was defined as any response of a patient to a drug that was unintended and undesired by the prescribing physician. - Only documented and probable ADRs were included.	- ADR - sex - race - number of drugs - atopy or past ADR - renal and hepatic disease - Infection - GI disease	- Incidence of ADR: 10.8% - Age was not a determinant. - Number of drugs and ADR%: 0-5 …… 4.2% 6-10 ……7.4% 11-15 …… 24.2% 16-20 ……40.0% 21+ ……45.0% Total 10.8% - Risk increased for black men, patients with infection, renal and gastrointestinal problems. - Increase risk of ADR for atopy and prior ADR	Cause and effect between ADR and number of drugs or mortality were not clear due to temporality issues.
Zopf *et al.*; 2008 (312)	A prospective multicenter study based on intensive pharmacovigilance in three hospitals. - 2,371 patients (Germany)	No exclusion	- Patient charts were screened, and bedside visits took place for detection and evaluation of potential ADRs. - Naranjo algorithm was used to evaluate potential ADRs.	- ADR detected by Naranjo criteria excluding doubtful cases.	- 33% of patients developed one or more potential ADRs. - Female (OR 1.60, CI 1.31–1.94), - Age (per 15 years: OR 1.12, CI 1.05–1.19) - Number of drugs (OR 1.145, CI 1.13–1.17). - Weight, height and body mass index were not predictors.	Multiple reactions within a patient were ignored.
Spriet *et al.*; 1977 (271)	France wide prospective study where Physicians were randomly selected from all regions of France. - A total of 22277 patients taking Cosadon® (pentifylline and nicotinic acid) were included.	No exclusion	- Possible side effects were taken as ADR (tolerance to treatment); all adverse or unexpected effects were recorded with the associated drugs and their dosage.	- side effects - sex - age - weight - region - dosage - duration - therapeutic result	- 13.8% possible side effects - 15.2% (females) vs. 11.9% males - Age was a factor (10.5% for < 30 years and 16.3% for 80+ years - Lower weight was a risk factor where rate was 20.7% for <30 kg and 13.2% for >90 kg - Geographical region: Paris (16.2%) vs Mediterranean (10.7%) - Duration of treatment: 26.5% (1 month treatment) vs. 10% (3 months treatment)	There was no causality assessment.

Table 2.2. (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Budnitz *et al.*, 2006 (313)	Active surveillance from January 1, 2004, through December 31, 2005, through the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project on individuals treated in ED - Over 2-year 21,298 ADR cases	No exclusion	- An adverse drug event case: an incident emergency department (ED) visits for a condition that the treating physician explicitly attributed to the use of a drug or a drug-specific effect. - If a condition is specifically linked to a drug in this section, then the case is included.	- ADE detected by physicians at ED - Direct attribution of ADE by the physician was needed.	- 2.4 individuals / 1000 population treated in ED and 16.7% of which hospitalized due to ADE. - ADEs accounted for 2.5% of emergency department visits for all unintentional injuries and 6.7% of those leading to hospitalization. - RR, 2.4; 95% CI, 1.8-3.0 (aged 65 years or older vs. younger. - CNS, systemic anti-microbial, hormone-modifying, hematologic, oncologic, and cardiovascular agents accounted for 70% of the ADEs.	Only few determinants of ADE were evaluated.
Gandhi *et al.*, 2000 (286)	Patient survey and retrospective chart review on randomly selected outpatients in eleven Boston-area ambulatory clinics - 2,248 outpatient adults (USA)	No exclusion	- Patient-reported events were defined as drug complications - ADR identified by nurses were verified by physicians with Naranjo criteria	- Patient-reported drug complications and ADEs - Patient satisfaction - Risk factors: age, sex, race, level of education, language and insurance status	- 18% of patients reported a drug complication and chart review identified ADR in 3%. - Patient survey identified 91% of the events and chart review identified 15%. - Independent predictors of drug complications: number of medical problems, failure to explain side effects, and primary language other than English or Spanish. - 5% of the patients with ADR were hospitalized and 13% had a documented previous reaction to the causative drug.	Patient-reported drug complications were not evaluated for causality. So comparison with the method involving nurse/physician is not possible.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Curb *et al.*, 1985 (314)	The Hypertension Detection and Follow-Up Program, a community-based clinical trial of 10940 hypertensive patients randomly assigned to usual care or to an intensive stepped-care program of antihypertensive treatment - 10940 hypertensive patients - 3844 new hypertensive patients	Only anti-hypertension drugs were studied	Only ADR which were severe enough to discontinue drug therapy were considered. ADR were graded into possible and definite and probable	- Side effects severe enough to cause discontinuation of drug treatment - Risk factors: race, sex, age category	- For 32.7% of the new hypertensive patients, drug treatment was discontinued due to side effects and 40% had more than one ADR. - Possible ADR = 23.4% - Definite or probable = 9.3% Risk factors: - White male = 40.9% - White female = 33.7% - Black male = 26.6% - Black female = 22.9% - Age group (60-69 yrs) had the lowest rate of ADR. - Only 3% required outpatient therapy for the ADR in addition to the discontinuation.	The 'elderly group' might be more fit than the younger groups and might represent a healthier subset of the elderly patient population.
15. Gurwitz *et al.*, 1988 (290)	An anticoagulation clinic at the University of Massachusetts Medical Center (1978 to 1986) - 321 patients	Patient on warfarin	Bleeding complications were assessed from the patient and classified as minor or major based on requirement of hospitalization, transfusion or discontinuation of therapy	- Minor or major bleeding complications - Risk factors: age, sex, indication for anticoagulant, duration of follow-up, specific medical problems, total number of medications, previous warfarin exposure, intensity of follow-up,	- 19% and 4.4% of patients developed minor and major bleeding complications, respectively. - risk of bleeding increased for the first two years of anticoagulation - Multivariate analysis: lack of an association between age and risk of bleeding after accounting for previous warfarin exposure, total number of medical problems, and total number of medications.	The sample size was limited.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Tanner *et al.* 1988 (276)	Spontaneous reporting of ADR maintained by the US government FDA during 1986 The population of the USA	- No dug was excluded	The ADR were reported by health professionals and consumers	- ADR reporting rates and adjustment by drug consumptions (drug mentions)	- ADR reports for < 65 years: 74/million population and for ≥ 65 years: 159/million population - ADR reports for < 65 year: 20/million drug mentions and for ≥ 65 years: 13/million drug mentions	No other covariate was considered and no causality assessment for the reported ADR.
Landefeld *et al.*, 1989 (270)	Prospective follow-up of 562 patients discharged from a university hospital receiving warfarin (197–1983) Patients where warfarin was indicated for different conditions	- Warfarin only	Major and minor bleedings	- Major and minor bleedings were explicitly defined using objective criteria - Risk factors: age, history of stroke, history of GI bleed, serious comorbid condition, AF, systolic BP, prothrombin time	- 24% of patients developed major (12%) and minor (12%) bleeding and 2% died. - ≥65 years of age, history of stroke, history of gastrointestinal bleeding, serious comorbid condition, atrial fibrillation, high systolic pressure, prolonged prothrombin time were independent risk factors for major bleeding	Number of drug was not included as a risk factor.
Walker *et al.*, 1980 (315)	Hospital-based study on patients receiving Heparin - 2656 patients receiving heparin in a hospital for	- Heparin (the study drug) and ASA as a covariate were included.	Major and minor bleeding	- Bleeding was characterized clinically and divided into two groups. - Risk factors: age, sex, heparin dose and frequency, renal function, alcohol consumption, aspirin intake	- risk of bleeding (crude) = 9% - Aspirin use and being female were a risk factor in both minor and major bleedings. - Dose of heparin was a risk factor for minor bleeds and alcohol consumption was for major bleeds.	Comorbid conditions and concomitant drugs other than aspirin were not included.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Caamano *et al*., 2005 (283)	All patients admitted to the participating centers in 1991, 1993, 1995, 1997 and 1998 were enrolled and followed until discharge. 83 centers throughout Italy participate in the project and every region had at least one center.	No drug was excluded	- A questionnaire was completed on admission. - The Naranjo criterion was used to assess causality.	- Prevalence of ADR - Risk factors: gender, age, level of education, family members, alcohol and tobacco use, renal and liver disease, comorbidity, number of drugs, and mental test score	- 4.27% ADR rate at the time of admission. - Significant predictors of ADR include poor nutritional condition, more than 2 drugs prior to hospital admission and renal disease. - Poor cognitive condition was negatively related to ADR. - Sex, age, level of education, smoking or alcohol use, and number of medical conditions were not predictors of ADR.	Cross-sectional study: difficult to infer causality. Measurement of education could be represented with more categories.
Onder *et al*., 2002 (281)	All patients admitted to the participating centers in pre-specified periods of 1991, 1993, 1995, and 1997were enrolled and followed. 81 centers throughout Italy participate in the project and every region had at least one center.	No drug was excluded	The Naranjo criterion was used to assess causality.	- ADR and severe ADR were outcome variables. - Risk factors: age, sex, alcohol and tobacco use, Charlson-comorbidity index, number of drugs	- Rate of ADR was 3.4% - Female, alcohol drinker and number of drugs increased the risk of ADR while age, smoking, and Charlson-comorbidity were not predictors. - Older age groups, patients with more drugs and more comorbid conditions had higher risk of severe ADR.	As Caamano *et al*.(previous)
Tran *et al*., 1998 (316)	ADR clinic at Sunnybrook Health Science Centre, Canada from 1986-1996 - 2367 patients	No drug was excluded	Potential adverse events reported by patients were verified clinically through blood tests or biopsies, skin testing and oral challenges	ADR and severe ADR	- 74.1% of the patients referred to the Drug Safety Clinic were females. - Mean age: 47±17 years	No data available about the source for the females, their drug usage pattern, how different or similar with their male counterparts.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Camargo *et al*., 2006 (282)	Five internal medicine units in a university hospital located in Southern Brazil (2001) 333 patients were monitored	No drug was excluded	Intensive monitoring of ADR using medical records	- ADR verified by Naranjo criteria - Risk factors: - age, sex, length of hospitalization, number of diagnoses, number of drugs (before and after admission)	- ADR rate = 43% and 25.9% including and excluding 'possible ADR" category, respectively. - Risk factors: - number of drugs before hospitalization: OR, 95% CI; 2.93 (1.69, 5.06) - number of drugs after hospitalization: OR, 95% CI; 2.3 (1.19, 4.45) - >7 days of follow-up: 2.93 (2.08, 7.82) - age, sex and number of diagnoses were not predictors of ADR.	Mix-up of outpatient and hospital developed ADRs; inclusion of follow-up time as a predictor might be a problem on cause-effect relationship.
Bates *et al*., 1999 (291)	Two large tertiary care hospitals in Boston (USA) in 1993 - cohort: 2379 total admissions - case-control: 247 ADEs and 4108 admissions	No drug was excluded	Drug incidents were identified using nurses and pharmacists and these incidences were reviewed by two physician reviewers.	- ADE verified by physician reviewers - preventable ADE - Severe ADE - Risk factors: Age, sex, insurance, hospital service (medical/surgical), race, BUN, creatinine, albumin, AHFS class, number of drugs, number of AHFS drug, comorbidity, ICU admission	- 139 ADE in 2379 patients; 32 preventable ADE - Increased risk of preventable ADE with AHFS class (platelet, antidepressant, antihypertensive, and electrolyte) and medical ward admittance (cohort study) - Age, sex, comorbidity, number of drugs before and after admission, presence of altered mental state, abnormal renal function test were not predictors of ADE or preventable ADE. - Exposure to psychoactive and cardiovascular drug were predictors of ADE.	There were few ADEs, resulting in low power to detect important covariates.

Table 2.2. (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Zopf *et al.*, 2008 (279)	Prospective study in internal medicine departments of two university hospitals (Germany) which underwent intensive pharmacovigilance 907 patients were monitored	No drug was excluded	The Naranjo criterion was used to assess causality.	- All ADRs except doubtful cases - Risk factors: - age, sex, alcohol and nicotine use, vital signs, lab data, number of drugs	- ADR prevalence = 38% - Risk factors: OR, 95% CI - Sex, 1.6 (1.0, 2.4) - Body temperature, 1.7 (1.2, 2.3) - Erythrocyte count, 0.4 (0.2, 0.9) - Thrombocyte count, 0.7 (0.6, 0.9) - No. of drugs, 1.1 (1.07, 1.16)	Multiple reactions within a patient were ignore and no distinction was made on the occurrence of ADR whether in-hospital or outpatient; Temperature and erythrocyte and thrombocyte count might be the product of the ADR rather than predictors of ADR (temporality is an issue)
Honigman *et al.*, 2001 (305)	All patient visits to primary care practices using the electronic records (170 clinicians), Boston (USA) - 15,665 patients	No drug was excluded	Potential ADEs were identified by a computer algorithm (specific ICD-9 codes, allergy rules, text searching) and chart review was the gold standard	Samples of the incidents identified by the computer algorithm were verified manually by the investigators.	- ADE rate = 5.5 per 100 patients per year and 9.1% of ADEs resulted in hospitalization. - Naranjo classification of ADE: - possible: 12% - probable: 53% - definite: 37.7% - Patients with ADE had twice as many new drugs prescribed and were taking nearly three times the number of drugs ($p<0.01$) - Antihypertensives, antibiotics and diuretics were responsible in 56% of the ADEs. - Dermatologic, CNS, and GI events were the most common.	This is a one center study and the generalizability of the findings is limited.

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Jacubelt *et al.*, 1990 (274)	Patients admitted to a German teaching hospital from 1980 - 1987. - 70,500 admissions	No drug was excluded.	Intensive drug monitoring system involving a clinical pharmacologist and an internist during ward rounds to collect ADR reports from physicians and ward staff.	ADR according to WHO definition	- 17.9% patients had ADR (Males: 16.5%; Females: 19.9%) - ADR rate increased with age (<19 years: 8.9%; >60 years: more than 20%) - Rate of ADR was consistently higher for females than males for age groups greater than 30 years. - Rate of ADR increased with number of prescribed medications and it was consistent irrespective of age (1-4 drugs: 3.2%; >29 drugs: 40%)	Multivariate analysis would be ideal to show the effect of number of drugs while controlling for age.
Trifiro *et al.*, 2005 (269)	ED visits in 22-hospitals located in all regions of Italy (2000). - 188854 patients who visited an ED in Italy.	No drug was excluded	ADR with the exclusion of intentional drug abuses	All patients were evaluated by a 'committee' for the occurrence of ADR. Informal causality assessment involving temporality, symptoms, patient's perception, and previous published studies on the drug-symptom relationship were used. Risk factors: age, gender	- 3.3% of the total ED visits and 13.8% of drug users were ADR related. - Predictors of ADR (multivariate): - age 60-75 years: 1.96 (95%CI: 1.14–3.38) - age >75 years: 3.86 (95%CI: 2.14–6.96) - sex was not a significant predictor, 1.32; 95%CI: 0.94–1.86).	Causality assessment was suboptimal; omission of important covariates in multivariate analyses (number of drugs and comorbidities)

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Sarkar *et al.,* (280)	Two nationally representative sample surveys: the National Ambulatory Medical Care Survey and the National Hospital and Ambulatory Medical Care Survey (2005-07) - Sample size of 1,628. - extrapolated to adult (≥ 18 years) adult population (270.5 million)	No exclusion	- Question with a focus on ADE: "Is this visit related to adverse effect of medical/surgical care or adverse effect of medicinal drug?" - Two physician reviewers reviewed the diagnostic and reason for visit (RFV) codes for all candidate visits.	-Visit level: geography, OPD/ED, primary/non-primary; - Patient level: age, race, gender, insurance, # of drugs, comorbidities.	- ADE visits constituted 0.5% of all ambulatory visits with 72% occurred in OPD and 28% in ED. - ADE visit rates increased with age. - Age and comorbidity are not predictors of ADE once number of medication was included. - The number of drugs was the only significant predictor in multivariate analyses. - The uninsured and under-insured had fewer ADE visits. - More ADE visits occurred in primary care than specialty care.	ADE identification was suboptimal: patient and physician unrecognized ADEs were left out. There is no validation of ICD-9 codes and no report on the performance of the codes. Only a maximum of 8 drugs were captured. Medication discontinued at the visit was not captured.
16. Begaud *et al*., 2002 (285)	Spontaneous reports of ADR in the French pharmacovigilance database from January 1995 to December 2000 with the population base of the French population (58.5 million in 1999)	No drug was excluded	The ADR were reported to the French pharmacovigilance unit and have causality and seriousness assessment	- Age-specific ADR reporting rates - Risk factors: drug consumption per 10-years age group	- 92,043 spontaneous reports of ADR: an average reporting rate of 2.62 per 10,000 persons per year (2.46 for men and 2.79 for women) - 1.94 per 10,000 persons per year for < 60 years and 5.13 per 10,000 persons per year for ≥ 60 years - after adjustment for drug consumption, there was no relationship between age and ADR rates and peak rates ADR were for 30-39 years of ages.	ADR definition depends on spontaneous report which is known to have high rate of under-reporting..

Table 2.2 (Continued) Review of studies that included risk factors of adverse drug events in adult patients

Study	Data source, setting and population	Drugs included	Definition of adverse drug reaction or events	Primary and secondary outcomes and risk factors	Result	Limitation
Pomerantz *et al*., 2004 (317)	Patients form a single HMO who filled at least one prescription of antidepressant during the first 4-months of 2001 (incident cases)	New and old antidepressants	Discontinuation of antidepressant: filling less than 4 prescriptions in 6 months were considered discontinuation.	Discontinuation rate and duration of intended treatment Risk factors: Prescriber intent and diagnosis - Off-label status was considered as a determinant of treatment discontinuation.	- Depression and depression plus anxiety were the diagnoses in 52% of the patients. - Primary care physicians were prescribers for 70%. - Prescription filled at least 4 times in 6 months: 55% vs 29% for depression and other diagnosis, respectively - TCA, bupropion, trazodone, diagnoses other than depression and anxiety, primary care physician were risk factors for discontinuation of antidepressant treatment. - SSRI, depression, anxiety, multiple prescriber, and female sex are protective factors for discontinuation of antidepressant treatment.	Discontinuation of treatment was considered result of patient action and adverse drug reaction was completely disregarded. Treatment switches were not considered in the overall assessment.

Chapter 3: Methods

Definition of terms: adverse drug event and adverse drug reaction

The thesis reviewed studies from the 1960s up to the present. Terminologies and their operationalization have changed over this time period and new terminologies were also created by drug regulatory bodies and researchers. In 1972, WHO's defined adverse drug reaction (ADR) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" (318). The definition for ADR did not change however reporting requirements have changed to give emphasis to serious and life threatening ADRs (319). The restrictive nature of the definition of ADRs which exclude inappropriate use of a drug and errors such as wrong dose or route which resulted in harm, patient safety research introduced new term called adverse drug event (ADE)(320). ADE was originally defined as "an injury resulting from medical intervention related to drug" in the 1990s' (321) and the definition was adopted by Institute of Medicine. The researchers who defined the term later simplified it to "an injury resulting from the use of a drug" (322). ADE includes all adverse drug reactions and it also includes injuries due to medication errors such as prescribing, dispensing and administration errors. For example, harm caused by overdoses and duplication therapy are ADEs but do not qualify as ADRs since overdoses are not "normally used doses". As a result, we elected to use ADE as the outcome variable which encompasses the broadest range of drug-related events areas which may result in patient injury. While, ADE does not require a causal link between the drug and the event, discontinuation of a drug due to an adverse drug event by the treating physician implied a stronger link even if the drug and the event were not subjected to a formal assessment of likelihood of causal assessment.

In the previous chapters, the different pharmacosurveillance tools currently available for pharmacoepidemiologic evaluations of drug use and their drawbacks especially involving off-label use of drugs was discussed. In addition, the drug life-cycle emphasizing the roles of the patient, the physician, the drug regulatory bodies, and the pharmaceutical companies in off-label prescribing and use of drugs was described, along with specific drugs involved in

extensive off-label use and their consequences. Moreover, studies which evaluated off-label prescribing in adult population, their findings and their limitations and the limited studies available which associate off-label use with adverse drug events were reviewed. At the same time, electronic health records are heralded as the means of tackling the problem of under-reporting of adverse drug reactions, measuring and documenting important clinical and epidemiological variables which would facilitate the evaluation of drugs' use and their effects.

Organization of Methods of the thesis

First, the electronic health record used to generate the data and its features which allow monitoring and follow-up of drugs according to their use will be described. Second, the methods used to validate the treatment discontinuation and treatment indication features in the EHR (manuscript 1 and 2) including the statistical analyses will be summarized. Third, the patients and prescriptions assembled to evaluate the prevalence of off-label prescribing and the three levels of determinants including drug, patient and physician levels and the statistical method used to analyze three level nesting data with a binary outcome - drugs within patients and patients within physician (manuscript 3) will be outlined. Finally, the cohort assembled to investigate the association between off-label use and adverse drug events will be described (manuscript 4).

The Quebec health insurance agency

The Régie de l'assurance maladie du Québec (RAMQ) manages the health insurance beneficiaries that represents 99% of the Quebec population and maintains a database that documents and updates name, age, sex, and residence of the beneficiaries. The RAMQ also manages reimbursement to physicians and pharmacies. Approximately 85% of physicians work fee-for-service and this generates information for each health care encounter including the date of the patient's visit, diagnosis, type and location of service and provider. In addition, the RAMQ public drug insurance program covers 50% of the population including the elderly, welfare recipients, and persons not insured through their employer and this generates validated data on medication, date dispensed, prescribing physician, quantity and duration of prescription (71).

Medical Office of the XXI Century (MOXXI)

The Medical Office of the XXI Century is an electronic heath record system created in 2000 to optimize the planning and delivery of primary health care and at the same time to address lack of resources for ambulatory physicians (323). The system allows physicians to prescribe drugs electronically and to check automatically for drug-drug, drug-disease, drug-age, and drug-allergy contraindications depending on user-selected alert filtering mechanism. Through integration with the RAMQ, the system allows physicians to access clinical data including patient's dispensed drugs, health problem list and allergy list and recent hospitalization and emergency department visits.

Physicians were eligible for inclusion in MOXXI research program if they practiced in selected geographical locations in Montreal and Quebec City, were remunerated on a fee-for-service basis, and worked in office-based practice three or more days per week. Overall, 410 physicians met these criteria, and 113 (27.6%) physicians consented to participate. On average, participating physicians are 5 years younger than non-participating physicians. The mean rate of electronic prescribing was 36.9 prescriptions per 100 visits in the first 20 months post-implementation (47). Physicians were more likely to use the system for patients who had more complex drug therapy, higher fragmentation of care, more emergency

department visits, and a greater number of prescribing physicians (324;325). Recruitment and retention of physicians as well as patients is a dynamic process where physicians and patients can enter or leave the cohort during the study period.

The treatment discontinuation and dose change features of MOXXI

Physicians using the MOXXI system can order the discontinuation of a drug or change a dose; and this information printed on the prescription (Figure 3.1 and Figure 3.2). Reasons for drug discontinuation or change in dose must be completed for each treatment change order. Physicians select from a menu of standard options including adverse drug reaction, ineffective treatment, drug interactions, adjusting dose to optimize treatment, error in prescribing, incorrect medication dispensed, end of treatment, simplifying treatment, substitution for less expensive drug, and temporary discontinuation. Starting from September 2009, a new feature in MOXXI was added which asks physicians to document the ADE responsible for the discontinuation of the drug. Drug-specific adverse drug events previously identified for the drug are supplied in a drop-down menu and physicians can also select from the global list of ADE or can text-in the ADE (Figure 3.3).

The treatment indication feature in MOXXI

One important feature of the MOXXI system is a mandatory requirement for physicians to select at least one treatment indication for each prescribed drug from a list of approved (on-label) indications and unapproved (off-label) indications. Treatment indications are specific to each drug and can be selected from a drop-down menu or entered manually using free-text entry (Figure 3.4). The purpose of entering treatment indication is to document, in standard format, data that are used to populate the patient's health problem list. Entering the treatment indication at the time of prescribing will also be used to provide computerized decision-support for drug-disease interactions and chronic disease management. Physicians can change the status of a particular health problem(s) to inactive, excluding those from the drug-disease interaction monitoring after the problems are resolved or successfully treated. There are more than 2540 unique drugs and 1249 unique treatment indications in the system. The list of drugs and therapeutic indications for a drug is updated monthly by the commercial provider (Vigilance Santé©) through ongoing review of drug monographs, compendia and published studies (326).

Patient health problem list

MOXXI has a capacity to generate automated patient-specific health problem list from three sources including treatment indications recorded at the time of drug prescribing using the MOXXI system, diagnostic codes from medical service claims and dispensed single indication drugs which point to specific health problem. In addition, physicians can also add problems to the list by searching a global list. Physicians can validate the problems that originated from diagnostic codes and single indication drugs as valid or not valid (Figure 3.5). In a 2009 study (327), 72% of these problems were found to be valid by the treating physician and it was found out that health problems which needed care and drug management on continuous bases were more likely to be validated.

The drug profiler

The patient drug profile contain a graphical representation of all drug therapies for the past 6 months (prescribed/dispensed, stopped or continued), medical services used, drug cost information, emergency department visits and hospitalizations. It allows the physician to visualize much needed information with a capacity to investigate further; for example the reasons for the drug discontinuations. Re-prescribing or stopping a drug can be initiated from this window directly (Figure 3.6).

Figure 3.1 Drug discontinuation and dose change feature of the MOXXI EHR system. (one list of reasons for stopping a drug and changing a dose of a drug)

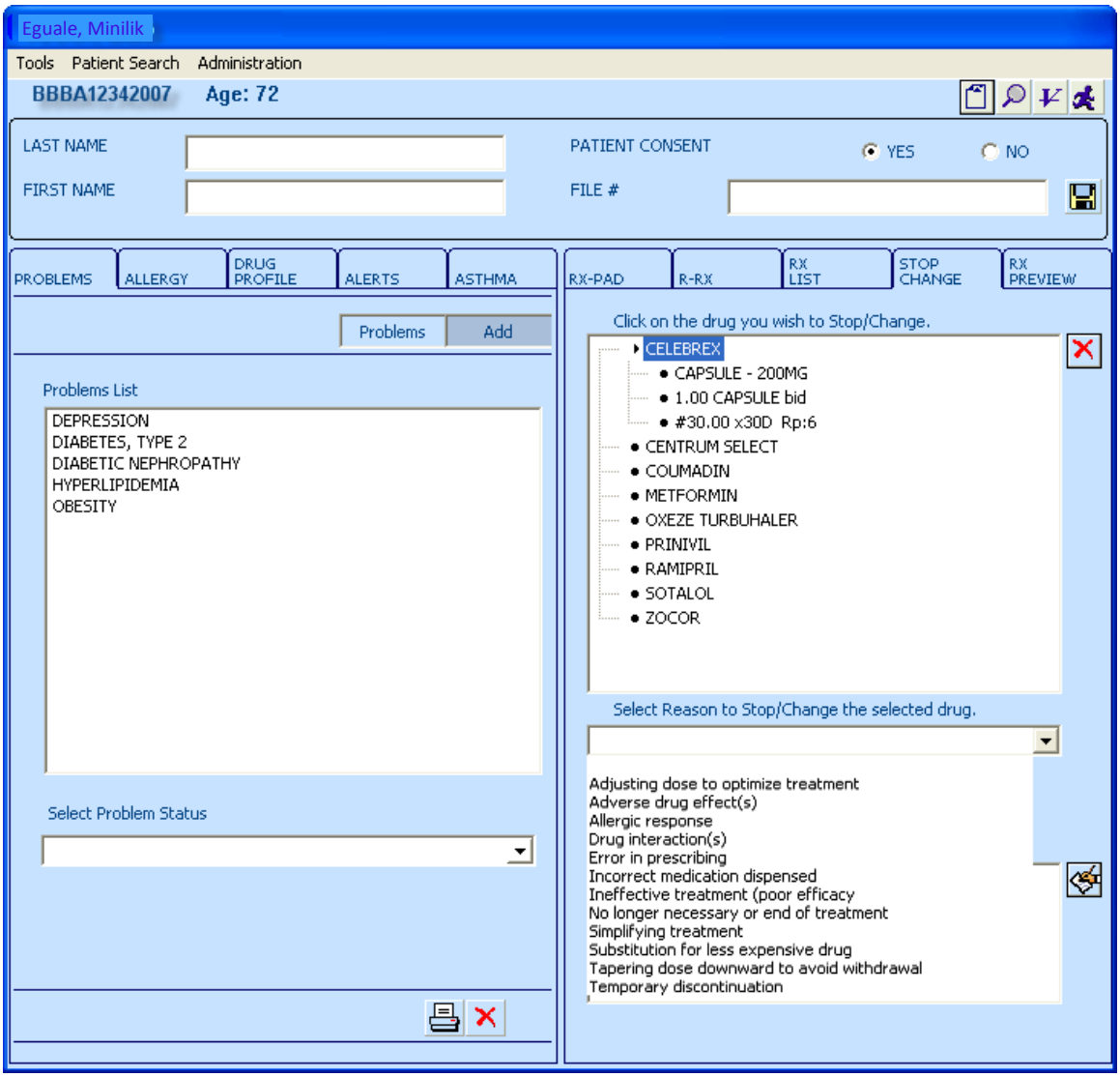


Figure 3.2 Drug discontinuation and dose change feature of the MOXXI EHR system. (only reasons for drug discontinuations shown)

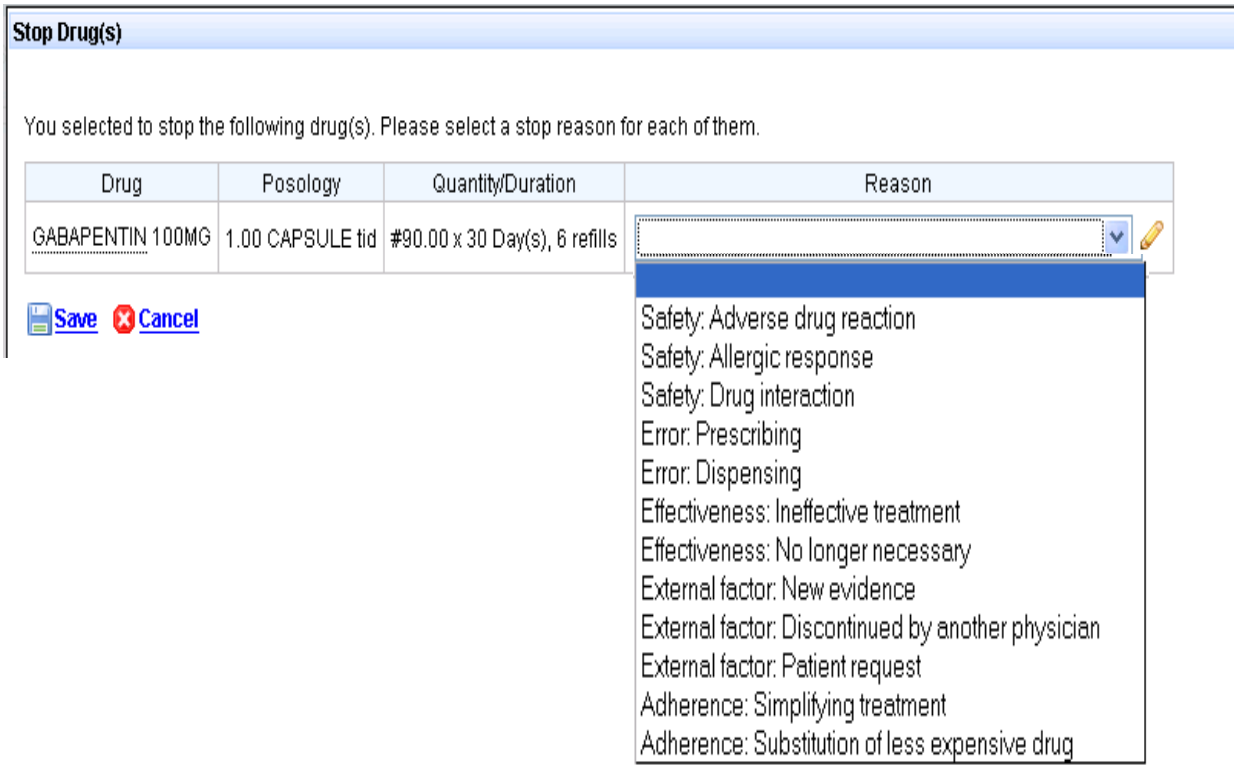


Figure 3.3 Adverse drug event documentation in MOXXI EHR.

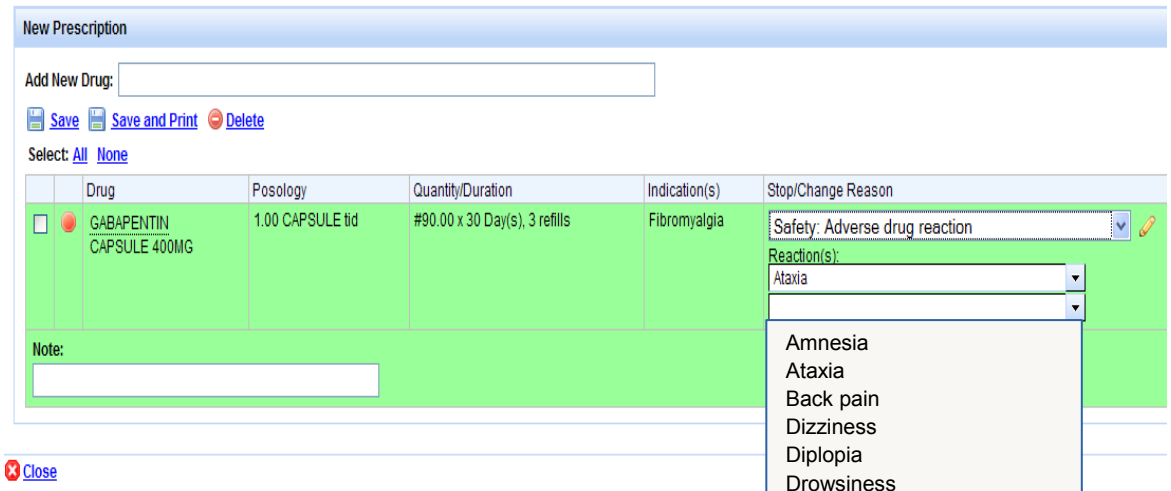


Figure 3.4 Documentation of treatment indication in the MOXXI EHR system.

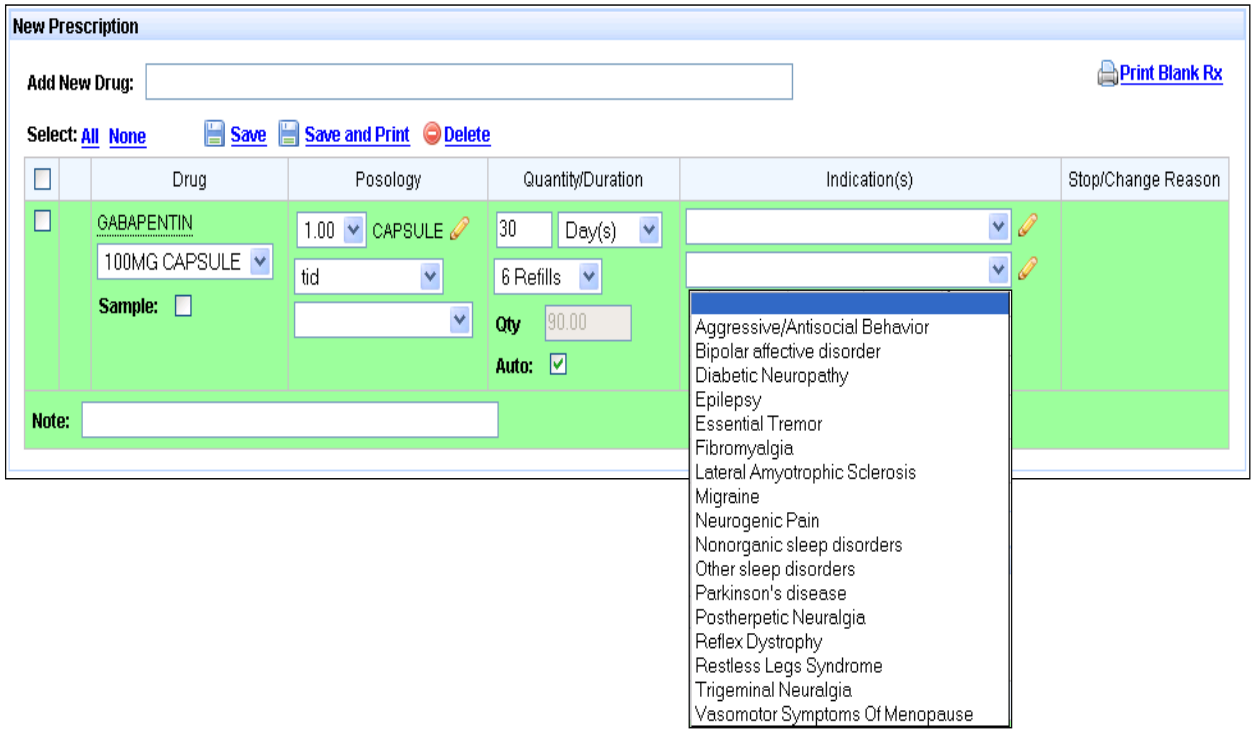


Figure 3.5 Patient problem lists displayed in MOXXI EHR system.

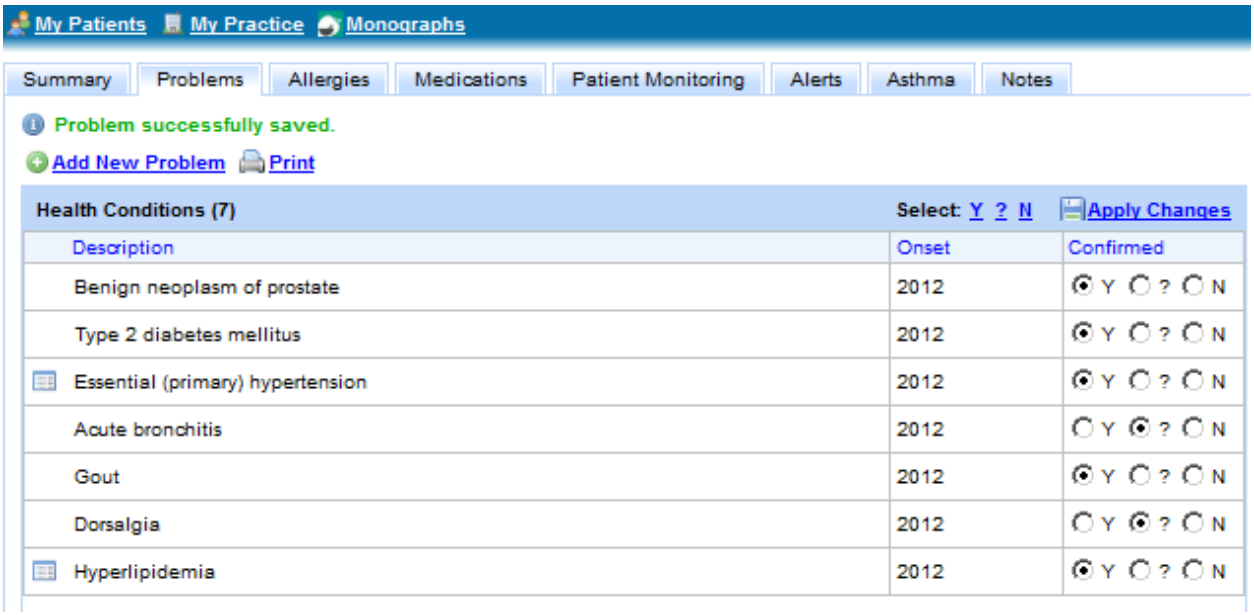
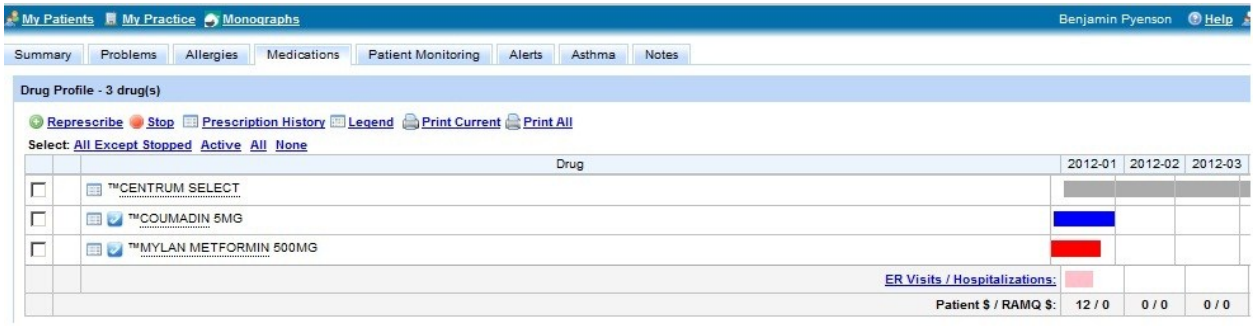


Figure 3.6 The drug profiler of MOXXI EHR system.



Methods for manuscript 1 and 2

Validation of treatment discontinuation and dose changes (manuscript 1)

The accuracy, sensitivity, specificity, positive and negative predictive value of the MOXXI system in documenting prescription drug discontinuation and dose change orders was assessed by comparing information obtained from the MOXXI system with information from physician-facilitated chart review. The sensitivity provided an estimate of the extent to which all treatment changes for the targeted drugs were recorded by the computerized prescribing system whereas the specificity provided an estimate of the extent to which physicians would erroneously record treatment changes that had not occurred.

Design and study population

The study was conducted in the first 22 physicians of the 104 enrolled at the time who had used the MOXXI electronic prescribing system, in order to ensure that the validity of treatment change orders were not be confounded by differences in physician experience using the MOXXI system. Patients were eligible for this study if they had made a visit to a study physician between December 5, 2005 and March 30, 2006 and received an electronic prescription for a chronic condition. Medications prescribed for episodic conditions (anti-infectives, ear, eye, nose and throat drugs, skin and mucous membrane preparations and vitamins) and drugs with frequent changes in dose (anti-coagulants) were not eligible because these drugs are supplied for a limited time and most anti-coagulants dose change occur by telephone without the patient visiting a physician.

Assessment of drug discontinuation and dose-change orders in the EHR.

All patients with an electronic drug discontinuation or dose-change order during the study period were included. An equivalent number of patients without treatment change orders were randomly sampled for each physician on each day that treatment change orders were documented. To improve study efficiency and decrease cost, a one-to-one sampling ratio between treatment change order positive and negative visits was used (328). The sample size was calculated using an estimated sensitivity of 75% and an incidence rate of treatment change of 8 per 100 electronic prescriptions. To obtain a 95% confidence interval for sensitivity within 10% of the true value, we calculated that we would need a sample size of

600 visits with 300 treatment change positive visits and 300 treatment change negative visits. An automated database query was developed to identify, on a daily basis, the patients with a treatment change-positive visit for eligible drugs. For each treatment-change positive visit, we developed another query to sample one treatment change-negative visit for each physician that occurred on the same day of each treatment change-positive visit.

Gold standard: Physician-facilitated chart review.

One of the challenges in conducting chart review in primary care is that the documentation is typically not as extensive as hospital charts. As much as 10% of diagnostic and treatment decisions and 70% of patient education is not recorded in the primary care medical chart (329). To address this problem, two healthcare professionals conducted a physician-facilitated chart review within 24 hours after the visit. During the interview a chart review was carried out. By using this approach, we increased the likelihood that the physician was able to recall undocumented details of the patient situation, thereby providing a more complete assessment of treatment changes. The automated database query that flags a drug discontinuation or dose change was used to identify patients in whom a treatment change had occurred. Sampled patients' visits were identified by the physician's name, patient's name, age, sex, unique identifier, visit date and time. Reviewers were blinded to treatment change status and the reasons.

The interviews were carried out each time a patient pair (one treatment change-positive visit; one treatment change-negative visit) was identified. The interviewers arranged with the physician's receptionist for the medical charts to be available to the physician during the interview process and an interview for the pair carried out at the same time. Neither physicians nor the interviewers were allowed to open the MOXXI application at the time of the interview. Physician interviews were conducted by two health professionals after training and standardization. A structured questionnaire was used to determine if a patient had drug discontinuation or dose change. With each treatment change reported by the physician, the reason for the treatment change was requested and spontaneous responses were documented. The physician was then asked to identify which of the reasons listed in the application (e.g. adverse drug reaction, ineffective treatment, adjust dose to optimize

treatment) was the main reason for the treatment change. Interview data were entered into a computerized database and later linked to the MOXXI data file with treatment change status.

Statistical analysis

Sensitivity, specificity, PPV and NPV of electronic drug discontinuation and dose change orders were estimated. Sensitivity was defined as the proportion of actual treatment change-positive visits documented in physician-facilitated chart review that were correctly identified by the MOXXI electronic prescribing system. Specificity was defined as the proportion of actual treatment change-negative visits that were correctly identified by the MOXXI electronic prescribing system. Naïve sensitivity and specificity that were uncorrected for sampling fraction of patients with and without a treatment change order were calculated. These estimates were corrected to address the over-sampling of treatment change-positives that would introduce verification bias (overestimation of sensitivity and underestimation of specificity). Adjustment for verification bias was done by multiplying the treatment change-positive and -negative groups by the inverse of the selection probability. In general, adjustment for verification bias results in a decrease in the sensitivity and an increase in the specificity measures (330). 95% Confidence intervals (CI) were constructed using the logit method of Begg-Greenes and Pepe (330;331). In verification biased sampling, the PPV and the NPV are unbiased. Multivariate logistic regression with a generalized estimating equation framework was used to determine if there were significant differences in the demographic and clinical characteristics of patients with and without a treatment change order. Physician was the clustering factor and an independent correlation structure was specified with robust standard error (332).

Validation of treatment indication feature of MOXXI (manuscript 2)

Treatment indication for a specific patient and drug was obtained from the physician with an open-ended request: "identify and describe the treatment indication for the drug you prescribed for this patient". Later, treatment indications provided by the physician for a given drug were coded as matching (yes/no) to the treatment indications recorded in the MOXXI database.

Three hundred and thirty-eight visits made by consenting patients in the year 2005 - 2006 were used to ascertain whether the treatment indication recorded by MOXXI was an accurate representation of the physician's intent documented in the patient chart. Health Canada's drug product database was used to identify on- and off-label indications for each drug (333).

Statistical Analysis

In data accuracy studies from computerized systems for diagnoses and health problems (334-337), two complimentary measures, the sensitivity and the PPV, provide answers to the two most important questions: the completeness and the correctness of the information captured by the electronic system, respectively. In this study, sensitivity was defined as the proportion of treatment indications documented in the medical chart (paper) that were correctly identified by the electronic prescribing system. PPV was defined as the proportion of treatment indications documented in the electronic system that were found to be correct by chart review. 95% CIs were constructed using the exact method for binomial proportions (338). The design of most research that assesses data accuracy does not allow the true negatives to be assessed. This is because true negatives may be infinitely large (335) (e.g. persons without hypertension or systemic lupus erythematosus). In our study, the true negatives represent the number of treatment indications that were not recorded by the electronic prescriber that should not have been recorded in the chart of the patient as well.

The discordance between the chart and electronic prescription documentation of treatment indication was analyzed qualitatively to assess the nature of differences in indications recorded. In addition, each drug-indication combination was classified as on- or off-label using Health Canada drug approvals, and then the proportion of off-label prescribing was estimated.

Methods for manuscript 3: Prevalence and determinants of off-label prescribing

Three features of the MOXXI EHR permit off-label use to be documented accurately. First, the system requires selection of a treatment indication for each electronic prescription from a menu of on-label and off-label indications (Figure 3.4). Second, therapeutic indications for a

specific drug are updated monthly by a commercial vendor through review of drug monographs, compendiums, and published studies (326). Third, unlisted off-label indications can be entered in a free-text field. To enhance the value for clinicians of recording treatment indication, two useful features are provided. First, documented treatment indications are used to populate the patient's problem list. Second, the history of drugs used with each treatment indication is recorded, including drug discontinuations and dosage changes, along with the reason for treatment failures (e.g. hypotension) (339). As a result, the drug-treatment indication data have been shown (340) to be highly accurate, with a positive predictive value of 97% and sensitivity of 98.5%. The objective of manuscript 3 was to evaluate the prevalence off-label use and assess drug, patient, and physician factors that influence off-label prescribing.

Design and Study Population

A total of 650,237 electronic prescriptions were written between January 2005 and December 2009 and a total of 253,347 unique patient and drug indication combinations were identified after repeated prescriptions were removed, representing 50,823 patients, 113 physicians, and 684 drugs.

Off-label use: definition and operationalization

Each prescription was classified as on-label or off-label according to the Health Canada drug approval database (333). Indications were considered to be Health Canada approved (i.e., on-label) if they could be matched to the therapeutic indication reported in the drug's package insert as of December 2010, regardless of dosage, frequency, route of administration, duration of treatment, and patients' age range. Any indication that could not be matched to the labeled indication was considered off-label. For each off-label drug indication pair, the level of evidence supporting the drug's overall efficacy was categorized with the DrugPoints System, which uses the same drug information as DrugDex (both Thomson Reuters). These systems, which are used by Medicare/Medicaid to determine reimbursement for drugs (341), describe the relationship between drug and treatment indication using three dimensions: level of efficacy (effective, favors efficacy, inconclusive, or ineffective), strength of recommendation (for all patients, most patients, specific patients, or not recommended), and strength of evidence (randomized controlled trial [RCT] with consistent results, RCT with

inconsistent results, or no RCT). We followed a published algorithm (33), and used these dimensions to determine whether there is strong scientific evidence for the off-label use of a drug for a particular treatment indication. Strong evidence exists when (1) the drug is effective or favors efficacy for a particular treatment indication, (2) the drug is recommended for most or all patients with the treatment indication, and (3) the studies used to evaluate efficacy and the strength of evidence included at least one RCT (33).

Potential risk factors for off-label prescribing

Drug characteristics: We measured *drug class* as a potential risk factor for off-label use because research (18) has shown that medications approved for psychiatric and allergy indications are more likely than other agents to be prescribed off-label. Drugs were classified using the American Hospital Formulary Service (AHFS). *Drug age*, defined as the year the drug was approved for marketing, was included because drugs that have been on the market longer have had a greater opportunity for off-label use. *Drug age* was categorized into three groups (before 1981, between 1981 and 1995, and after 1995) because the specific year could not be found for drugs approved before 1981 and 1996 was taken as mid-year between 1981 and 2009. The *number of approved indications for a drug*, defined as a count of Health Canada-approved indications, was included because drugs with fewer approved indications may have a higher likelihood of being prescribed off-label.

Patient characteristics: Age, sex, and co-morbidity (Charlson Comorbidity Index) were assessed because older patients and those with a co-morbidity may be less likely to receive off-label prescriptions owing to higher risks of adverse events (268). Pharmacokinetic and pharmacodynamics factors differ between males and females (292), resulting in varied responses to certain drugs (293), which may increase the chance of receiving prescriptions for off-label drugs (216).

Physician characteristics: We measured three physician characteristics. *Years* since *graduation from medical school* was used as a proxy for physicians' knowledge of drugs. Older physicians are more likely to use drug detailers as a source of drug information, and, therefore, may be more likely to prescribe off-label (191;342). *Physician sex* was included because male physicians are more likely to prescribe new drugs than are female physicians

(173;343). We hypothesized that physicians who follow evidence-based medicine would be less likely to prescribe off-label. We used the evidence scale from the Evidence-Practicality-Conformity questionnaire (344). This scale predicts clinical guideline compliance and measures the extent to which a physician prefers scientific evidence as the best source of knowledge in clinical decision making (e.g. on-label prescribing) compared with clinical experience or opinion leaders (344;345). High scores in the evidence scale indicate an evidence-based orientation.

Statistical analysis

The prevalence of off-label prescriptions was calculated by dividing the number of off-label prescriptions by the total number of prescriptions for a given drug, drug class, and overall. In addition, off-label use was partitioned into off-label with and without strong scientific evidence. The prevalence of off-label use without strong scientific evidence was calculated using off-label prescriptions as a denominator.

To assess determinants of off-label use, a multi-level approach was used, with prescription (drug-indication pair) being the unit of analysis. Drug, patient, and physician characteristics represented the three levels in the analysis and clustering of drugs within each patient and patients within physician was accounted for using alternating logistic regression, a multilevel analytic approach for binary outcomes (346-348). In alternating logistic regression, within-patient and within-physician clustering is described with pair-wise odds ratios (ORs) rather than intra-class correlations. Two outcome variables were evaluated: off-label status (yes/no) and off-label status without strong evidence vs. on-label and off-label status with strong evidence.

Methods for Manuscript 4: Off-label use as a determinant of adverse drug events

Design and Study Population

To evaluate the association between off-label use and adverse drug events, a prospective cohort of 46,294 patients prescribed new (incident) medication was assembled between

January 1 2005 and December 30 2009. A drug prescription was considered incident if it had not been prescribed or dispensed in the past 12 months. Patients were followed from the date of the prescription to the date the drug was discontinued or the end of treatment or the end of follow-up (December 30 2010).

Adverse Drug Event (ADE)

Adverse drug events were defined as drug discontinuations made by physicians with the given reason being "*adverse drug reaction*" or "*allergic reaction*". Prior evaluation of the validity of these data found a concordance of 85.7% between the electronic documentation of adverse drug reaction and the medical chart (339). Overall drug therapy was changed in 13.4% of patients. The proportion of ADE detected was 2.3%. Other reasons included optimizing treatment (3.6%), ineffectiveness (2.9%), prescribing and dispensing error (1.3%), no longer necessary or effective (1.8%), patient request (0.6%), simplifying treatment (0.4%), discontinued by another physician (0.3%) and substitution for less expensive drug (0.2%) were reasons to change drug treatment. ADEs documented in the MOXXI system were classified according Medical Dictionary for Regulatory Activities (MedDRA) which includes System Organ Classes (SOC) and Preferred terms (PT). SOCs represent the highest hierarchy that provides the broadest concept and PT is a distinct descriptor of sign, symptom, diagnosis, investigation or surgical or medical procedure.

Potential Risk Factors for adverse drug reaction

Off-label use

The definition of off-label use and its operationalization was the same as described in manuscript 3. There are two variables for off-label use: 1) on- or off-label and 2) on-label, off-label with strong scientific evidence and off-label without strong scientific evidence.

Drug characteristics: We measured *drug class* as a potential risk factor for ADE as prior research has shown that central nervous system, cardiovascular and anti-infective classes were more often implicated in ADEs (273;278;291;305). Drugs were classified using the American Hospital Formulary Classification (AHFS) system. *Drug age*, defined as the year the drug was approved for marketing, was included as ADEs of recently approved drugs were more likely to be reported than older drugs (306;307). Drug age was categorized into three

groups (before 1980; between 1980 and 1996; and after 1996 or recently approved drugs) because the specific year could not be found for drugs approved before 1981 and 1996 was taken as mid-year between 1981 and 2009.

Patient characteristics: We included age and measures of comorbidity (Charlson comorbidity index) as older patients (268-272) and those with more comorbidity (278;283;284;286) may exhibit higher risks of ADE. Patient sex was included because higher rates of ADE were reported for females than males (279;281;297;349). *Number of drugs* the patient is taking was included since it was shown to be the most important risk factor for ADE (21;272;274;278-284). *Continuity of care* (COC) index was included to correct for possible surveillance bias in the opportunity to detect ADEs as patients with better continuity have fewer emergent visits (300;350) possibly because both ADEs and disease exacerbations are more likely to be detected and averted by the primary physician responsible for care. COC index was defined as the ratio of number of a patient's visits to the primary care physician to the square root of the total outpatient visits a patient had in a 12-month window and the index was calculated using the medical services claims (351). The 'square root of the total outpatient visits' gives more weights to patient with more visits and assigns a higher COC index.

Statistical Analyses

The incidence rates of drug discontinuations due to ADR for participants were calculated by dividing the number of incident cases by the number of person-months of follow-up. Person-months were calculated per drug starting from the first day of prescription up to the date of drug discontinuation or the end of the study (December 30, 2010). The hazard ratio (HR) was calculated dividing the incidence rate in one category by the incidence rate in the reference category. The unit of analysis was drug; and drugs were nested within patients. The marginal Cox model for clustered data was employed with a robust sandwich covariance estimate to account for the intra-cluster dependence for both univariate and multivariate analyses and to construct 95% CIs (352;353). The two off-label variable indicators were included in the Cox model one at a time. Proportionalities of the hazard rates were analyzed by testing covariate-time interaction terms and using Schoenfeld and Martingale residuals and

inspecting the various survival curves (354). As a sensitivity analyses and for comparison purpose a marginal Poisson regression model was also employed.

Ethics

The MOXXI research program was approved by the provincial privacy commission, the legal counsel of the provincial health insurance agency, the Quebec College of Physicians, and the McGill University, Faculty of Medicine Institutional Review Board (Project identifier: A01-B02-02A). All patients and physicians are consented to be part of the research program.

Chapter 4. Detection of adverse drug events and other treatment outcomes using an electronic prescribing system

Preamble to manuscript 1

The aim of this manuscript was to determine the accuracy of the MOXXI EHR system in documenting orders for drug discontinuation and dose changes of prescription drug treatment; and to identify the reasons for drug discontinuation and dose-change of medications. The motivation for this study was the inefficiency of current pharmacosurveillance methods in identifying adverse drug events and other treatment outcomes described in the first section of the background ("Challenges in the Post-Market Surveillance of Prescription Drugs"). In principle, all physician-initiated treatment changes can be documented. Reasons for discontinuing or changing drug doses, such as adverse drug events or ineffective treatment could be required as a mandatory field at the time of drug discontinuation, as has been done by the Partners group in Boston and the MOXXI group in Quebec. Reports could be collected automatically and analyzed systematically to calculate the incidence rate of adverse drug events and ineffective treatments, and to compare the rates of adverse events among different drugs in real-world patient populations. The development and standardization of these methods both nationally and internationally could enhance the amount and quality of data available for conducting accurate and timely evaluation of the safety and effectiveness of drugs. However, the first step was to validate this source of documentation of drug discontinuation and dose-change features in an electronic health record (MOXXI) against a gold-standard.

Title Page:

Title: Detection of adverse drug events and other treatment outcomes using an electronic prescribing system

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Abstract

Background

Current pharmacosurveillance methods do not provide timely information on drug safety and effectiveness. Real-time surveillance using electronic prescribing systems could address this problem; however the data collected using these systems has not been validated. We investigated the accuracy of using orders for drug discontinuation and dose change in an electronic prescribing system as a potential source of information for drug safety and effectiveness.

Objectives

To determine the accuracy of an electronic prescribing and drug management system in documenting orders for discontinuation and dose changes of prescription drug treatment, and in identifying the reasons for the drug discontinuation and dose change.

Study design and setting

We prospectively assessed the accuracy of electronic prescription orders for drug discontinuation and dose change by comparing them with treatment changes documented by physician-facilitated medical chart review (gold standard). Validity was evaluated in 620 patients of 22 community-based primary care physicians as well as the reasons for these treatment changes.

Results

A total of 141 (41.7%) drug discontinuation orders and 197 (58.3%) changes in drug doses were identified by chart review, the majority of which were for cardiovascular and central nervous system drugs. Ineffective treatment (30.8%), adjusting dose to optimize treatment (25.1%) and adverse drug reactions (21.9%) were the most common reasons for treatment change. The sensitivity of the electronic prescribing system in identifying physician-initiated

drug discontinuations and dose changes was 67.0% (95% CI: 54.1, 77.7) and the specificity was 99.7% (95% CI: 99.5, 99.9). The positive and the negative predictive values of electronic treatment discontinuation and change orders were 97.3% (95% CI: 95.6, 98.7) and 95.8% (95% CI: 92.9, 97.7), respectively.

Conclusion

An electronic prescribing and drug management system documents drug discontinuation and dose-change orders with high specificity and moderate sensitivity. Ineffective treatment, dose optimization and adverse drug reactions were the most common reasons for drug discontinuation or dose changes. The electronic prescribing system offers new method for augmenting pharmacosurveillance.

Introduction

Adverse drug events are among the leading causes of death (4) at annual cost of more than $US 177 billion dollars (355). Post-marketing surveillance is crucial to quantify previously recognized adverse drug events, to identify unrecognized adverse drug events, to evaluate the effectiveness of the drugs in real world situations (32), and to decrease mortality and morbidity associated with adverse drug events.

Although evidence supporting the safety and effectiveness of drugs is required before a drug is approved, the data typically come from randomized controlled trials conducted with a limited number of patients who are selected carefully to optimize compliance and limit comorbidity (6-8). This population of patients often does not represent the typical patient treated with the drug after its approval. Moreover, the use of surrogate end points (e.g. change in weight or change in blood sugar level) may not confer expected benefits for clinically relevant long term outcomes (e.g. stroke, myocardial infarction, mortality) (356). Challenges in the evaluation of drug safety and effectiveness are compounded when drugs are used off-label. Off-label prescribing is estimated to occur in one-third to one-fifth of prescriptions (18;19). As a result, there may be different effectiveness and safety profiles of drugs in the post-market patient population.

The need for new and innovative pharmacosurveillance methods

Spontaneous reporting has been a successful method of identifying some serious adverse drug events within months of the drugs' approval (49;357). However, known limitations of spontaneous reporting include systematic under-reporting which was estimated to be in the range of 90-98% (6;10-12), lack of denominators to estimate incidences, and delay in detection (6;10). Prescription event monitoring (PEM) is a more recently developed method for pharmacosurveillance that requires physicians to respond to a follow-up questionnaire on patients' response to new drugs (15) while making no cause-effect association between the drug and the adverse drug event. PEM has an average response rate of 53% (range 35% - 65%), however only 28% of physicians respond when more than 30 patient questionnaires are sent to a single physician (14;15). The labor intensive nature of data collection makes the method unsustainable for a nation-wide and routine surveillance (52) which is essential to

detect adverse drug events rapidly. Neither spontaneous reporting nor PEM are aligned to the day-to-day activities of physicians, especially primary care physicians, who are responsible for the majority of prescriptions written (16).

Lessons may be forthcoming from public health. Efforts to engage front-line practitioners in mandatory disease reporting as a front-line surveillance tool have been replaced or supplemented with electronic surveillance through the secondary use of electronic "point-of-care" information systems. Laboratory, pharmacy, population health information centers, and emergency department triage and treatment systems are mined to identify notifiable diseases, symptom clusters, and emerging epidemics (63;65). There is an opportunity to use a similar strategy in pharmacosurveillance that addresses the current problems of under-reporting of adverse drug events and lack of timely data without adding to physicians' practice burden.

Electronic prescribing and drug management systems

A common area of focus in Canada, Europe, Australia, New Zealand, and the United States is the implementation of electronic prescribing and integrated drug management systems. This is because it is widely accepted that computerization of drug management will reduce avoidable errors in prescribing and dispensing (35-37;358). Primary care physicians in Denmark, UK, and New Zealand are leaders in electronic prescribing with more than 90% of prescription written electronically (359;360). Although US and Canada have lagged behind other nations in the adoption of electronic prescribing (16;360), new regional and national investment initiatives should rectify this situation (34).

Transmission of orders to discontinue medication to dispensing pharmacies and monitoring of patient treatment outcomes, two features of computerized prescribing systems, are considered to be important to improve drug safety and effectiveness (37;40). Reasons for discontinuing or changing a dose of a medication could be added as a mandatory field to electronic drug discontinuation orders. This information could be used to augment the detection of potential adverse events in conjunction with spontaneous adverse drug event reporting systems and PEM (39;44;45). Requiring physicians who utilize electronic prescribing to enter reasons for drug discontinuation or dose changes, such as adverse drug

reaction or ineffective treatment could enable such data to be rapidly collected and analyzed systematically as part of a pharmacosurveillance system. These data could be used by regulatory agencies to estimate the incidence of potential adverse drug events and ineffective treatments, and to compare the rates of adverse events among different drugs in real-world patient populations. The development and standardization of these methods nationally and internationally could greatly increase the data available to signal potential efficacy and safety problems early in the post-marketing phase and may lead to a more thorough and directed investigation of the drugs involved.

The feasibility of such a method of treatment outcome monitoring and the validity of the information generated by electronic prescribing systems has not been investigated. The aims of this study were to determine the accuracy of an electronic prescribing and drug management system in: (i) documenting orders for drug discontinuation and dose changes of prescription drug treatment; and (ii) identifying the reasons for the drug discontinuation and dose-change of medications.

Context

An integrated electronic prescribing and drug management system (Medical Office of the XXI century [MOXXI]) was developed by the clinical and health informatics research group at McGill University, in Montreal, Quebec, Canada, and implemented in a population of primary care physicians (family physicians) to study the effects of computerized systems in primary care (47). Similar to other electronic prescribing systems (361), physicians can document a patient's drug, disease, and allergy profile and write and transmit prescriptions. Through interfaces with pharmacy and provincial insurance systems, MOXXI physicians can retrieve recent emergency department visits, and hospitalizations, information on all dispensed prescriptions, and all health problems identified in medical services claims by themselves and other physicians. Additional features of MOXXI include preloading and integration of patient demographic information, automated alerts for potential drug interactions and drug disease and allergy contraindications.

Physicians using the MOXXI system can order the discontinuation of a drug or change a dose; and this information is sent electronically to the dispensing pharmacy and is printed on

the prescription (Figure 3.1). Reasons for drug discontinuation or change in dose must be completed for each treatment change order. Physicians select from a menu of standard options including adverse drug reaction, ineffective treatment, drug interactions, adjusting dose to optimize treatment, error in prescribing, incorrect medication dispensed, end of treatment, simplifying treatment, substitution for less expensive drug, and temporary discontinuation.

Physicians were eligible for inclusion in MOXXI research program if they practiced in selected geographical locations in Montreal and Quebec City, were remunerated on a fee-for-service basis (approximately 85% of Quebec physicians), and worked in office-based practice three or more days per week. Overall, 410 physicians met these criteria, and 113 (27.6%) physicians consented to participate. On average, participating physicians are 5 years younger than non-participating physicians. The mean rate of electronic prescribing was 36.9 prescriptions per 100 visits (interquartile range: 14.0; 45.0) in the first 20 months post-implementation (47). Physicians were more likely to use the system for patients who had more complex drug therapy, higher fragmentation of care, more emergency department visits, and a greater number of prescribing physicians (324;325).

Methods

The accuracy, sensitivity, specificity, positive and negative predictive value of the MOXXI system in documenting prescription drug discontinuation and dose change orders was assessed by comparing information obtained from the MOXXI system with information from physician-facilitated chart review. The sensitivity provided an estimate of the extent to which all treatment changes for the targeted drugs were recorded by the computerized prescribing system whereas the specificity provided an estimate of the extent to which physicians would erroneously record treatment changes that had not occurred.

Design and study population

The study was conducted in the first 22 physicians of the 104 enrolled who had used the MOXXI electronic prescribing system, in order to ensure that the validity of treatment change orders were not be confounded by differences in physician experience using the

MOXXI system. Patients were eligible for this study if they had made a visit to a study physician between December 5, 2005 and March 30, 2006 and received an electronic prescription for a chronic condition. Medications prescribed for episodic conditions (anti-infectives, ear, eye, nose and throat drugs, skin and mucous membrane preparations and vitamins) and drugs with frequent changes in dose (anti-coagulants) were not eligible because these drugs are supplied for a limited time and most anti-coagulants dose change occur by telephone without the patient visiting a physician.

Assessment of drug discontinuation and dose-change orders within the electronic prescribing system.

All patients with an electronic drug discontinuation or dose-change order during the study period were included. An equivalent number of patients without treatment change orders were randomly sampled for each physician on each day that treatment change orders were documented. To improve study efficiency, a one-to-one sampling ratio between treatment change order positive and negative visits was used (328). The sample size was calculated using an estimated sensitivity of 75% and an incidence rate of treatment change of 8 per 100 electronic prescriptions. To obtain a 95% confidence interval for sensitivity within 10% of the true value, we calculated that we would need a sample size of 600 visits with 300 treatment change positive visits and 300 treatment change negative visits. An automated database query was developed to identify, on a daily basis, the patients with a treatment change-positive visit for eligible drugs. For each treatment-change positive visit, we developed another query to sample one treatment change-negative visit for each physician that occurred on the same day of each treatment change-positive visit.

Gold standard: Physician-facilitated chart review.

One of the challenges in conducting chart review in primary care is that the documentation is typically not as extensive as hospital charts. As much as 10% of diagnostic and treatment decisions and 70% of patient education is not recorded in the primary care medical chart (329). To address this problem, an interview with the physician was carried out within 24 hours of the patient's visit by two healthcare professionals after training and standardization.

During the interview a chart review was carried out. By using this approach, we increased the likelihood that the physician was able to recall undocumented details of the patient situation, thereby providing a more complete assessment of treatment changes. The automated database query that flags a drug discontinuation or dose change was used to identify patients in whom a treatment change had occurred. Sampled patients' visits were identified by the physician's name, patient's name, age, sex, unique identifier, visit date and time. Interviewers were blinded to treatment change status and the reasons for treatment change.

The interviews were carried out each time a patient pair (one treatment change-positive visit; one treatment change-negative visit) was identified. The interviewers arranged with the physician's receptionist for the medical charts to be available to the physician during the interview process and an interview for the pair carried out at the same time. Neither physicians nor the interviewers were allowed to open the MOXXI application at the time of the interview. A structured questionnaire was used to determine if a patient had drug discontinuation or dose change. With each treatment change reported by the physician, the reason for the treatment change was requested and spontaneous responses were documented. The physician was then asked to identify which of the reasons listed in the application (e.g. adverse drug reaction, ineffective treatment, adjust dose to optimize treatment) was the main reason for the treatment change. Interview data were entered into a computerized database and later linked to the MOXXI data file with treatment change status.

Data analysis

Sensitivity, specificity, PPV and NPV of electronic drug discontinuation and dose change orders were estimated. Sensitivity was defined as the proportion of actual treatment change-positive visits documented in physician-facilitated chart review that were correctly identified by the MOXXI electronic prescribing system. Specificity was defined as the proportion of actual treatment change-negative visits that were correctly identified by the MOXXI electronic prescribing system. Naïve sensitivity and specificity that are uncorrected for sampling fraction of patients with and without a treatment change order were calculated. These estimates were corrected to address the over-sampling of treatment change-positives and avoid verification bias (overestimation of sensitivity and underestimation of specificity). Adjustment for verification bias was done by multiplying the treatment change-positive and -

negative groups by the inverse of the selection probability. In general, adjustment for verification bias results in a decrease in the sensitivity and an increase in the specificity measures (330). 95% Confidence intervals (CI) were constructed using the logit method of Begg-Greenes and Pepe (330;331). Multivariate logistic regression with a generalized estimating equation framework was used to determine if there were significant differences in the demographic and clinical characteristics of patients with and without a treatment change order. Physician was the clustering factor and an independent correlation structure was specified with robust standard error (332).

Ethics

The MOXXI research program on electronic prescribing and drug management in primary care was approved by the provincial privacy commission, the legal counsel of the provincial health insurance agency, the Quebec College of Physicians, and the McGill University, Faculty of Medicine Institutional Review Board. All patients and physicians are consented to be part of the research program.

Results

In the period from 5 December 2005 to 30 March 30 2006, there were 17,696 drugs prescribed electronically by study physicians. Among all electronic prescriptions, 1,435 (8.11%) were discontinued or the dose was changed using the treatment change feature in the MOXXI system. A total of 620 patients (310 with treatment change order and 310 patients without a treatment change order) were included in the study. Patients with treatment change orders were taking more medications than patients without treatment change orders and were more likely to have a diagnosis of hypertension, depression and insomnia (Table 4.1).

Drug discontinuation orders accounted for 41.7% of all treatment changes in drug therapy and the remainder was dose changes. Ineffective treatment (30.8%), adjusting dose to optimize treatment (25.1%) and adverse drug reactions (21.9%) were the most common reasons for changing drug treatment (Table 4.2). Drugs were discontinued most often

because of adverse drug reactions (43.3%) and ineffective treatment (29.8%). Most dose changes were increases in dose (70.8%) to optimize treatment (43.2%) or because treatment was ineffective (31.5%) (Table 4.2).

The majority of treatment change orders were for cardiovascular drugs (33.4%), central nervous system drugs (32%) and hormone and synthetic substitutes (19.8%) (Figure 4.1). Most cardiovascular drugs were anti-hypertensive (56.6%), followed by anti-lipemic agents (23%) and cardiac drugs (20.4%). Among the central nervous system drugs, treatment change orders were predominantly for antidepressants or antipsychotic drugs (59.2%). Ineffective treatment was the reason for treatment changes in 35.3% of cardiovascular drugs, 24.1% of central nervous system drugs and 73.7% of gastro-intestinal drugs. Adverse drug reactions were responsible for treatment changes in 23% of cardiovascular drugs, 19.4% of central nervous system drugs and 26.8% of hormone and synthetic substitutes. Drugs that were most frequently discontinued or modified were levothyroxine (14/73), amlodipine (13/62), and metformin (12/63) (Table 4.3). Adverse drug reactions reported included aching of muscle and numbness (atorvastatin) and dysphagia and dyspepsia (alendronate) (Table 4.4).

The sensitivity of the MOXXI application in identifying actual treatment changes of drugs was 96.2% and the specificity was 97.1% (Table 4.5). When the sensitivity and specificity were corrected for the sampling fraction (330;331), the corrected sensitivity was 67.0% (95% CI: 54.1, 77.7) and the corrected specificity was 99.7% (95% CI: 99.5, 99.9). The unbiased positive predictive value (PPV) was 97.3% (95% CI: 95.6, 98.7) and the unbiased negative predictive value (NPV) was 95.8% (95% CI: 92.9, 97.7).

The concordance between the reasons for drug discontinuation and dose change documented by the MOXXI application and the actual reasons reported in physician-facilitated chart review was 95.2% for ineffective treatment, 85.7% for adverse drug reaction and 80.8% for adjusting dose to optimize treatment (Table 4.6). The PPV of MOXXI application for identifying adverse drug reaction was 85.7% while ineffective treatment and adjusting dose to optimize treatment had PPV of 84.6% and 87.5%, respectively.

Discussion

We assessed the accuracy of drug discontinuation and dose-change orders documented in an electronic prescribing and drug management system to determine if this information could be used to identify physician-identified adverse drug events and other drug treatment outcomes. We found that physicians' drug discontinuation and dose-change orders can be recorded with excellent accuracy as can the reasons for the discontinuations and changes.

Concordance in reasons for treatment changes between the electronic prescribing system and the chart review was from 80.8% to 95.2% and could be improved by reducing the conceptual overlap of reasons for treatment changes. For example, a physician may indicate that a treatment was ineffective at a given dose and increase the dose to achieve the desired effect. In this case, both "ineffective treatment" at the current dose and "adjusting dose to optimize treatment" are accurate reasons for the physician's action. The creation of mutually exclusive categories and separate lists of reasons for dose changes and for drug discontinuations are two solutions that should address this problem. Moreover, the sensitivity of electronic prescribing systems could be improved with regulatory requirements for electronic prescribing, increased familiarity with the application and use of drug discontinuation, and dose-change features for all patients.

Blinding of the interviewers and the physicians as to the treatment change status of the patients' in the electronic prescribing system is one of the strong features of the study and helps to control observer bias and diagnosis review bias, respectively and provide unbiased results. The administration of physician-facilitated chart review soon after patients' visits is another strong feature that helps to decrease recall bias from the physicians.

Early introduction of computerized dispensing has paved the way for successful implementation of PEM in UK and New Zealand (52;362). Advances in electronic prescribing systems and electronic health records are enabling real-time collection of data on drugs and patients and creating an opportunity to evaluate the effectiveness and safety of drugs in a timely and unbiased manner. Electronic prescribing and data exchange by primary care physicians is widely adopted in Denmark and New Zealand. Although not all electronic prescribing systems provide mandatory documentation of treatment indication, and reasons

for drug discontinuation and dose-change, these features can be readily incorporated into existing systems. Electronic prescribing vendors and user have demonstrated the willingness and creativity to include new features to electronic prescribing systems (361;362). Furthermore, as standards and financing of computerization of health care is primarily determined by national and regional health authorities, certification processes for required features are already in place. The addition of the rational for treatment change orders could be readily included as a required feature for certification. Our study suggests there may be a substantial benefit to doing so. We showed that an electronic prescribing system can accurately document physician-identified adverse drug events better than spontaneous reporting system (363) and can be easily integrated into clinical work flow. Broad scale adoption of electronic prescribing nationally and internationally is critical, both to detect rare events and also to minimize potential biases from selective participation that may occur in both standard, and new forms of pharmacosurveillance. A pharmacosurveillance tool needs a sample size in the range of from 10,000 to 100,000 person-years of observations to detect rare adverse drug events which occur 3 in 10,000 and 3 in 100,000, respectively (364;365) and these sample sizes can be attained in relatively short period of time if electronic prescribing become legally mandated (Denmark) (366) or voluntarily introduced by legislative means such as with the U.S. Medicare Reform Bill (367).

One limitation of the study is that physicians were aware of the close monitoring of their behaviors during the study period. This could have resulted in a possible increase in the sensitivity of the system if they recorded more treatment changes during the study. However, the treatment change rate changed by less than 0.11% during the study period. In addition, the treatment change feature is considered to be an important feature by the physicians in clinical decision making because drugs discontinued or changed are included as part of the prescription. Medications prescribed for episodic conditions (e.g. anti-infective agents) may not be readily monitored through computerized prescribing systems since these drugs are supplied for a limited time and many treatment changes take place by telephone call-back to the physician or pharmacist. However, alternate approaches such as pharmacy call-back programs which are increasingly popular in community-based pharmacies may provide a follow-up service for new prescriptions that could fill this gap (368). Electronic treatment change orders will also not capture severe reactions and deaths. Yet, if electronic prescribing

systems could be combined with administrative data to determine mortality and hospital admissions, a more sensitive and comprehensive pharmacosurveillance system may be possible. Currently, an international effort to automate mortality statistics is underway to speed up registration of deaths and the availability of death data (369). Future studies should evaluate the added benefit of using electronic prescribing information linked with administrative data as a pharmacosurveillance tool. While our findings can not be extrapolated to all physicians, they may be generalized to clinical settings where electronic prescribing is mandatory and where physicians are well versed in using computerized prescribing system.

Timely data on the safety and effectiveness of drugs will enable regulatory bodies to evaluate drugs objectively, and identify drugs with suboptimal safety and effectiveness profiles in practice, and avoid unwarranted withdrawals of drugs on the basis of sporadic and incomplete evidence. Researchers, drug regulatory bodies, and the pharmaceutical industry should work together in shaping future directions of computerized prescribing systems to enable new opportunities for pharmacosurveillance.

Conclusion

Validation of an electronic prescribing and drug management system that documents drug discontinuation and dose change orders showed high specificity and moderate sensitivity. The electronic prescribing system offers new method for augmenting pharmacosurveillance. Our results provide strong evidence to support incorporating drug discontinuation and dose change orders as a required feature in integrated electronic prescribing systems to augment prescription event monitoring and spontaneous drug event reporting systems in signaling potential drug-related problems to target priorities for safety and effectiveness evaluations.

Table 4.1 The characteristics of patients who had drug orders for discontinuation and dose changes versus no change in drug treatment (no order for discontinuation or dose change).

	Status of treatment change by electronic treatment documentation		
Patient characteristics	**Yes (N=310)**	**No (N=310)**	**p-value***
	Mean (Median)	**Mean (Median)**	
Age	57.6 (60)	55.6 (57)	0.506
Number of drugs	4.0 (6)	2.6 (4)	0.0003
Number of medical problems	8.3 (9)	7.3 (6)	0.125
	N (%)	**N (%)**	
Female	193 (62.3)	201 (64.8)	0.576
Prevalent medical problems			
Hypertension	110 (35.6)	75 (24.1)	0.001
Hyperlipidemia	65 (20.9)	47 (15.2)	0.519
Hyporthyroidism	39 (12.4)	34 (11.1)	0.579
Depression	44 (14.2)	24 (7.7)	0.031
Insomnia	41 (13.1)	21 (6.9)	0.023

*Multivariate logistic regression under Generalized estimating equation framework with physician as a clustering variable.

Table 4.2 Reasons for treatment changes of drug identified by physician-facilitated chart review.

Summary reasons	Total N (%)	Dose Changes N (%)	Drug Discontinuations N (%)
Ineffective treatment	104 (30.8)	62 (31.5)	42 (29.8)
Adjusting dose to optimize treatment	85 (25.1)	85 (43.2)	0
Adverse drug reaction(s)	74 (21.9)	13 (6.6)	61 (43.3)
Error in prescribing	20 (5.9)	15 (7.6)	5 (3.6)
No longer necessary or end of treatment	17 (5.0)	1 (0.5)	16 (11.4)
Tapering dose downward to avoid withdrawal	15 (4.4)	15 (7.6)	0
Simplifying treatment	12 (3.5)	3 (1.5)	9 (6.4)
Substitution for less expensive drug	5 (1.5)	2 (1.0)	3 (2.1)
Drug interaction(s)	2 (0.6)	0	2 (1.4)
Incorrect medication dispensed	2 (0.6)	1 (0.5)	1 (0.7)
Temporary discontinuation	2 (0.6)	0	2 (1.4)
Total	**338**	**197 (58.3)**	**141 (41.7)**

Table 4.3 The most frequent drugs which were discontinued or dose changed.

Drugs	Therapy change	Dose Changes	Drug discontinuations
Synthroid (levothyroxine)	14	13	1
Norvasc (Amlodipine)	13	8	5
Metformin	12	11	1
Effexor (Venlafaxine)	11	9	2
Celexa (Citalopram)	9	6	3
Lipitor(Atorvastatin)	8	3	5
Hydrochlorothiazide	8	4	4
Pantoloc (Pantoprazole)	7	1	6
Diovan (Valsartan)	7	4	3
Elavil (Amitriptyline)	7	5	2
Wellburtin (Bupropion)	5	3	2

Table 4.4 The most frequent discontinued drugs with the reported adverse drug reactions.

Drugs	Adverse drug reactions (number of patients)
Lipitor (Atorvastatin)	aching of muscles (2) aching and numbness (1) dizziness (1)
Fosamax (Alendronate)	dysphagia and odynophagia (1) dyspepsia (1)
Mevacor (Lovastatin)	elevated liver enzymes (2)
Norvasc (Amlodipine)	Dizziness (1) excessive fatigue (1) leg swelling (1) severe constipation (1)
Elavil (Amitriptyline)	generalized itching (1) Drowsiness (1)
Ramipril	Cough (1)
Avandia (Rosiglitazone)	weight loss and diarrhea (1)
Celexa (Celexa)	Somnolence (1) sleepy and drowsy (1)
Metformin	Diarrhea (2) Nausea and upset stomach (1)
Effexor (Venlafaxine)	Insomnia (1)
Diovan (Valsartan)	Cough (1) low potassium level (1) dizziness and hypotension (1)

Table 4.5 Sensitivity and specificity of treatment change orders in the MOXXI electronic and prescribing system compared to physician-facilitated chart review (Gold standard).

	Chart-review		
Electronic prescribing system documentation	Treatment change positive	Treatment change negative	Total
Treatment change positives*	325	9	334
Treatment change negatives†	13	298	311
Total	338	307	645‡

Corrected for oversampling§	**Estimate**	**95% CI**
Sensitivity	67.0	54.1, 77.7
Specificity	99.7	99.5, 99.9

*Treatment change orders in the MOXXI system during patient's visit.

†Prescription orders where there is no treatment change order during patient's visit in the MOXXI system.

‡There were a total of 25 visits where two treatment change orders occurred in one patient's visit.

§The sensitivity and the specificity measures were corrected using the prevalence of treatment change orders in the MOXXI system (8.11%) during the study period with the method of Begg-Greenes(330) and Pepe.(331).

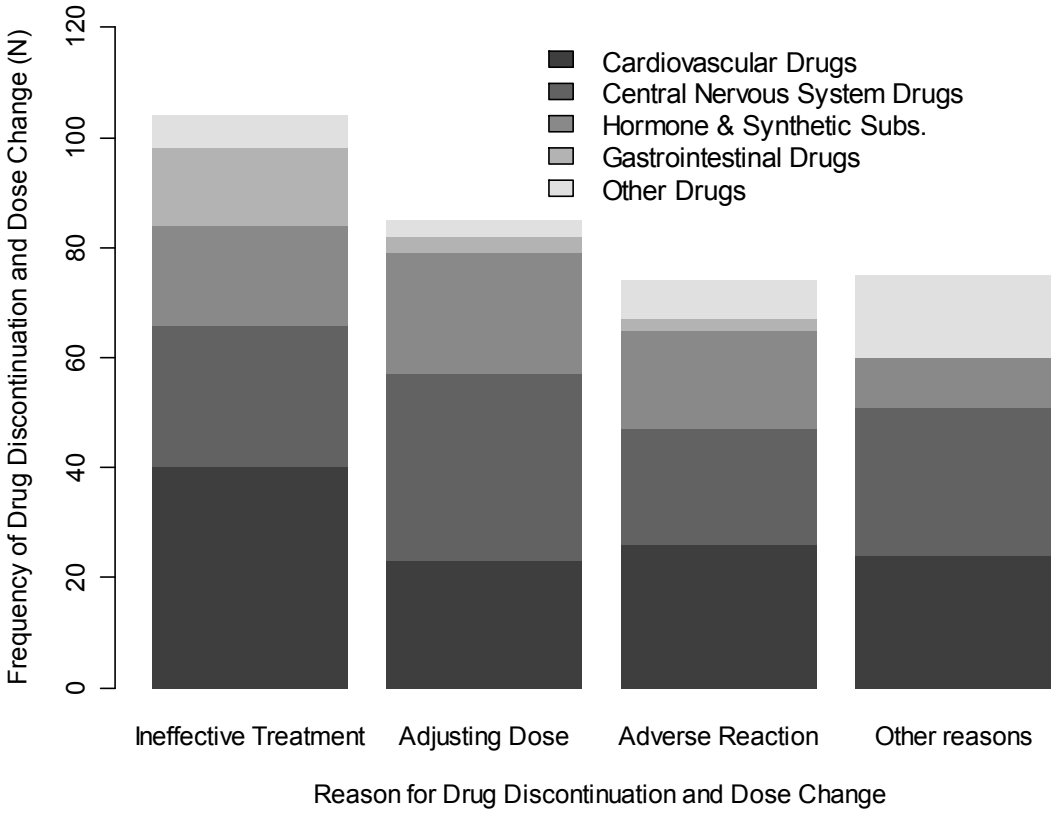
- Formula for the corrected sensitivity $= \dfrac{a}{a + c(w/(1-w))(p-/p+)}$
- w = the proportion of the sample with treatment change (MOXXI positive)
- 1- w = the proportion of the sample with no treatment change (MOXXI negative)
- p+ = the proportion of treatment change orders in the MOXXI system (population).
- p- = the proportion of orders with no treatment change in the MOXXI system (population)
- a = 325; c = 13 (from the table)

Table 4.6 Concordance in reason for treatment change orders from electronic prescribing system in comparison to physician-facilitated chart review.

	Reason documented in MOXXI system				
Reason from physician Interview	Adjusting dose to optimize treatment	Adverse drug reaction(s)	Ineffective treatment	*Other reasons	Total
Adjusting dose to optimize treatment	63	3	6	6	78
Adverse drug reaction(s)	1	60	6	3	70
Ineffective treatment	3	1	99	0	103
Other reasons	5	6	6	57	74
Total	72	70	117	66	325

* To simplify the table, other reasons (error in prescribing, no longer necessary or end of treatment, tapering dose downward to avoid withdrawal, simplifying treatment, substitution for less expensive drug, drug interaction, incorrect medication dispensed, and temporary discontinuation) were aggregated together. Drug interaction refers to the modification of a drug combination that may increase the risk of adverse event. If an adverse event (e.g. bleeding) did occur due to drug interactions, it would be recorded as an adverse event.

Figure 4.1 Frequency distribution of drug discontinuation and dose changes by drug class and by the reason for discontinuation or change.



- **Other drug classes** include autonomic drugs, smooth muscle relaxants, and blood formation.
- **Other reasons** include tapering dose downward, substitution for less expensive drug, error in prescribing, simplifying treatment, drug interaction, incorrect medication dispensed, and temporary discontinuation.

Chapter 5: Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic-prescribing: A validation study in Canada

Preamble to manuscript 2

The aim of this manuscript was to determine the sensitivity (completeness) and positive predictive value (correctness) of using the MOXXI EHR system to document treatment indications at the time of prescribing; and to investigate the use of treatment indication data in evaluating off-label prescribing in primary-care practice in relation to the second section of the background ("Off-label prescribing and use"). Lack of a direct link between drug and treatment indication was identified as the most important hurdle in monitoring off-label uses and their effect. Documentation of treatment indication would allow diagnosis-based reminders for drug selection, follow-up and safe drug dispensing. In the MOXXI EHR, documentation of treatment indication is a mandatory requirement for every drug prescription. However, the validity of using this approach to document treatment indications and whether the data allow assessment of off-label prescribing had not been investigated. Manuscript one and two will identify the two most important factors influencing drug treatment decisions: the reason for initiating a drug and the reason for discontinuing a drug or changing a dose of a drug – the life cycle of the drug.

Title Page

Title : **Enhancing pharmacosurveillance with systematic collection of treatment Indication in electronic-prescribing: A validation study in Canada**

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Abstract

Background: Adverse drug event reports used in pharmacosurveillance often lack complete information on treatment indication that is important for benefit-risk analyses and clinical and regulatory decision making. A systematic documentation of treatment indication using electronic prescribing applications provides an opportunity to develop new pharmacosurveillance tools that will allow evaluation of drugs by weighing benefits and risks for specific indications, and evaluate off-label prescribing. In addition, interfacing indications with reminders and clinical guidelines can enhance clinical decision making. We investigated the validity of treatment indications documented using an electronic prescribing system at the time of prescribing.

Objectives: To determine the sensitivity and positive predictive value (PPV) of an electronic prescribing system in documenting treatment indications at the time of drug prescribing, and to investigate the use of treatment indication data to evaluate off-label prescribing in primary-care practice.

Study Design and Setting: We prospectively assessed the validity of documenting treatment indication using an electronic prescribing system by comparing it with treatment indications documented by physician-facilitated medical chart review ('gold standard'). Sensitivity and PPV were evaluated in 338 patients of 22 community-based primary-care physicians in Quebec, Canada, in 2006.

Results: The sensitivity of the electronic prescribing system in documenting treatment indication was 98.5% (95% CI 96.5, 99.5) and the PPV of the system in accurately identifying the treatment indication was 97.0% (95% CI 94.2, 98.6). The treatment indication data collected using this system allowed assessment of off-label prescribing.

Conclusions: The electronic prescribing system offers a valid method for documenting treatment indication at the time of prescribing. Our results provide strong evidence to support incorporating mandatory recording of treatment indication in integrated electronic

prescribing systems to provide a critical piece of information for the evaluation of safety and effectiveness of drugs.

Introduction

Current pharmacosurveillance methods are slow and inadequate in addressing critical questions of drug safety and effectiveness (6;10). These methods are plagued by high rates of under-reporting of adverse drug events (ADEs) (10), including fatal ADEs (13). They also lack important clinical variables such as indication for treatment, risk factors (e.g. smoking, alcohol consumption), physical examination and laboratory indices (e.g. blood pressure, weight, glycosylated haemoglobin [HbA_{1C}]) and health outcomes (quality of life, functional status) that provide essential context for making rigorous safety and effectiveness decisions. In particular, the lack of information on treatment indication means that drugs are not evaluated in terms of their risks and benefits for a specific disease entity, but instead for all disease conditions where the drug may be prescribed (370-372).

Mandatory documentation of treatment indication at the time of prescription has several potential advantages, including the opportunity to generate diagnosis-based reminders for drug selection and follow-up, to incorporate clinical guidelines into the decision process, provide pharmacists with critical information for safe dispensing of drugs and appropriate patient counseling (373;374) and to create longitudinal drug treatment history (e.g. treatment failures by indication and their reasons). It will also enhance capacity for new automated pharmacosurveillance methods to be developed that assesses safety and effectiveness of drugs by treatment indication. Moreover, using such data will allow evaluation of the magnitude of off-label prescribing and its determinants with the associated safety and economic implications.

The feasibility of using electronic prescribing applications to retrieve treatment indication for prescribed medications through mandatory documentation and the validity of documentation at the time of prescribing has not been investigated. The aims of this study were to (i) determine the sensitivity and positive predictive value (PPV) of using an electronic prescribing system to document treatment indications at the time of prescribing; and (ii) investigate the use of treatment indication data to evaluate on- and off-label prescribing in primary-care practice.

Methods

Context

An integrated electronic prescribing and drug management system (Medical Office of the XXI century [MOXXI]) was developed by the Clinical and Health Informatics Research Group at McGill University and implemented in a population of primary-care physicians to study the effects of computerized systems in primary care in the province of Quebec, Canada (47). Similar to other electronic prescribing systems (361), physicians can document a patient's drug, disease and allergy profile, and write and transmit prescriptions electronically. Through interfaces with the provincial insurance system, MOXXI physicians can retrieve data describing recent emergency department visits, hospitalizations, dispensed prescriptions and health problems identified in medical services claims. All of these data are preloaded and integrated with patient demographic information, allowing the generation of automated alerts for potential drug-drug and drug-disease interactions or allergy contraindications. MOXXI physicians can order the discontinuation of a drug or change a dose. Reasons for these therapy changes are captured and the prescription can be sent either electronically or manually to the pharmacy. This drug discontinuation and dose-change feature was validated by chart review and found to have high specificity and PPV and moderate sensitivity (339).

One important feature of the MOXXI prescribing system is a mandatory requirement for physicians to select at least one treatment indication for each prescribed drug from a list of approved (on-label) indications and unapproved (off-label) indications. Treatment indications are specific to each drug and can be selected from a drop-down menu or entered manually using free-text entry (Figure 3.4). The purpose of entering treatment indication is to document, in standard format, data that are used to populate the patient's health problem list. Entering the treatment indication at the time of prescribing will also be used to provide computerized decision-support for drug-disease interactions and chronic disease management. Physicians can change the status of a particular health problem(s) to inactive, excluding those from the drug-disease interaction monitoring after the problems are resolved or successfully treated. Currently, there are 2540 unique drugs and 1249 unique treatment indications in the system. The list of drugs and therapeutic indications for a drug is updated

monthly through ongoing review of drug monographs, compendia and published studies (326).

Design and Study Population

Physicians were eligible for inclusion in the MOXXI research programme if they practiced in Montreal, were remunerated on a fee-for-service basis (approximately 85% of Quebec physicians) and worked in an office-based practice for 3 or more days per week. Overall, 410 physicians met these criteria, of whom 113 (27.6%) consented to participate (47). The study was conducted among 22 physicians who had 2 years' experience using the MOXXI electronic prescribing system. Since the aim of this study was to evaluate the routine capture of treatment indication using an electronic prescriber, we excluded recently trained physicians to ensure that the validity of treatment indication documentation was not confounded by differences in physician experience with the system.

Patients were eligible for this study if they had made a visit to a study physician and received an electronic prescription. We first sampled work-days for a particular physician, taking into account the number of days the physician was working and the availability of the physician for an interview. Whenever the physician could not be contacted within 24 hours, the particular prescription was replaced by another patient visit to the same physician. Three hundred and thirty-eight visits made by consenting patients in the year 2006 were used to ascertain whether the treatment indication recorded by MOXXI was an accurate representation of the physician's intent documented in the patient chart. Health Canada's drug product database was used to identify on- and off-label indications for each drug (333).

Physician-Facilitated Chart Review

One of the challenges in determining treatment indication is that health problems and treatments are documented but rarely explicitly linked. Moreover, as much as 10% of diagnostic and treatment decisions and 70% of patient education activities are not recorded in the primary-care medical chart (329). To address these two challenges, we conducted a physician-facilitated chart review by telephone ('gold standard') within 24 hours of the patient visit, to link drugs and indications and increase the likelihood that the physician was able to recall undocumented details of the patient visit.

Records of patients' visits included physician name, patient name, age, sex, unique visit identifier, visit date and time. Prior to the interview, the receptionist or the nurse was contacted to retrieve the respective charts. The interviewer confirmed that the physician had the chart available for reference before starting the chart review interview. Treatment indication for a specific patient and drug was obtained from the physician with an open-ended request: "identify and describe the treatment indication for the drug you prescribed for this patient". All treatment indications provided by the physician for a given drug were coded as matching (yes/no) to the treatment indications recorded in the MOXXI database.

In reviewing the patient chart, physicians were not allowed to open the MOXXI application during the interview so that they were not reminded what indication they had selected. Interviewers were also blinded about the treatment indication selected by the physician at the time of prescribing for a particular patient. Physician interviews were conducted by two health professionals after training and standardization. Interview data were entered into a computerized database and later linked to the data file with treatment indication.

Data Analysis

Characteristics of the patient population and treatment indications were summarized using descriptive statistics. In data accuracy studies from computerized systems (334-337), two complimentary measures, the sensitivity and the PPV, provide answers to the two most important questions: the completeness and the correctness of the information captured by the electronic system, respectively. In our study, sensitivity was defined as the proportion of treatment indications documented in the chart that were correctly identified by the electronic prescribing system. PPV was defined as the proportion of treatment indications documented in the electronic system that were found to be correct by chart review. 95% confidence intervals (CIs) were constructed using the exact method for binomial proportions (338). The design of most research that assesses data accuracy does not allow the true negatives to be assessed. This is because true negatives may be infinitely large (335) (e.g. persons without hypertension or systemic lupus erythematosus). In our study, the true negatives represent the number of treatment indications that were not recorded by the electronic prescriber that should not have been recorded in the chart of the patient as well.

The discordance between the chart and electronic prescription documentation of treatment indication was analyzed qualitatively to assess the nature of differences in indications recorded. In addition, each drug-indication combination was classified as on- or off-label using Health Canada drug approvals, and then the proportion of off-label prescribing was estimated.

Results

Among the 338 patients who made a visit in the study period, the average age was 58.2 years (median 60), 62.1% were females and, on average, patients had 8.3 medical problems (median 9) and 3.9 active drugs (median 2). The most common treatment indications identified in the study period were hypertension and depression, followed by pain and inflammation, and diabetes mellitus, respectively (Tables 5.1 and 5.2).

The sensitivity of the electronic prescribing system in documenting treatment indication was 98.5% (95% CI 96.5, 99.5) [Table 5.3]. For five drugs, the indications were entered manually and could not be interpreted. The PPV of the system in correctly identifying the treatment indication was 97.0% (95% CI 94.2, 98.6). Among the ten false positives, errors in selection (clicking a different indication than intended) is a probable cause in three cases since the correct indication was just above or below the incorrect indication but was not selected. Six of the incorrect indications shared pathophysiology or symptomatology with the correct indications obtained by the chart review; however, the chart-documented indications were not listed under the respective drug indication list. An example includes recording the indication 'pain' when the correct indication 'fibromyalgia' was not found in the list. This suggests that there is a tendency to select the conceptually closest indications when the correct one is not presented.

The sensitivity and PPV of the electronic prescribing system were 100% for hypertension, coronary heart disease, diabetes, hypercholesterolemia, osteoporosis, hypothyroidism and gastro-esophageal reflux. For depression, sensitivity was 100%, while PPV was 91.2%. Hormone replacement for menopause and andropause was documented with a sensitivity of

84.6% and a PPV of 100%. The system had 97.7% sensitivity and PPV for the indication pain and inflammation.

Of the 338 drugs, 28 (8.3%) were prescribed for off-label indications. The majority of these drugs were CNS agents (Table 5.4), including amitriptyline (indications: chronic pain and insomnia); gabapentin (indications: neurogenic and neuropathic pain) and clonazepam (indication: restless leg syndrome and anxiety). All drugs prescribed for hypertension, diabetes, hypercholesterolemia, osteoporosis and hypothyroidism were approved for these indications.

Discussion

This is the first study to assess the accuracy of treatment indication recorded at the point of care in an electronic prescribing application and to determine the utility of indication captured in this manner for assessing on- and off-label prescribing. We found that treatment indication was recorded with high sensitivity (completeness) and PPV (correctness) using an electronic prescribing system. Moreover, it was demonstrated that the treatment indication data could be used to assess whether the drug was prescribed for approved indications or was being used off-label.

To our knowledge, no study has evaluated the accuracy of an electronic prescribing system in documenting treatment indication at the time of prescribing. However, studies have been conducted on the validation of recording health problems in electronic medical records. A validation study of 41 practices in the General Practice Research Database that compared diagnostic information extracted from computer records against paper charts and patient interview reported a sensitivity of 75% and PPV of 100%; it also reported a sensitivity and specificity of 100% for diabetes and depression (334). A systematic review published in 2003 reported sensitivities of electronic health records ranging from 55% to 96% and PPV ranging from 96% to 100% in capturing health conditions (336). Generally, the MOXXI electronic prescribing system performed better than these systems because of the fact that the documentation of treatment indication was standardized for a specific drug, plus it was a mandatory requirement. Moreover, documentation of the treatment indication provided a

value-added benefit for the physician since this information is used to populate the patient's health problem list and all drugs are checked against the indication for possible drug-disease interaction. Entering an incorrect indication will also result in getting false drug-disease interaction alerts.

Our study shows that an electronic prescribing system that captures treatment indication can be used to assess the prevalence of off-label prescribing for all drug classes and medical conditions. Most off-label prescribing studies have focused on a single diagnosis or narrowly defined areas such as HIV, psychiatry or children, and only a few studies have estimated the overall magnitude of off-label prescribing by employing a sentinel survey of physicians (18;19). The treatment indication data can also be used to estimate prevalence of health problems, evaluate compliance to the standard of care, estimate compliance of drugs by indication, and to evaluate the safety and effectiveness of drugs for particular indications.

The study had a number of strengths. First, the administration of physician-facilitated chart reviews soon after patients' visits likely enhanced the accuracy of information about the treatment indication(s) for prescribed drugs. If chart review was done without the physician input, it would not have allowed us to link the drugs to the treatment indications since drugs and medical problems (or diagnoses) are written on the medical chart separately and linking would be even more difficult if the drug was prescribed for an off-label indication or for a previously undocumented indication. Second, blinding of the physicians and the interviewers to the treatment indication minimized possible observer and diagnosis review bias. Third, the distribution of treatment indications in this study is comparable to the distribution of treated health problems in Canada where the top eight indications in this study are among the ten top diagnoses treated with drugs (375). Because of the lack of published standards on how to design and report data accuracy studies (335), it was suggested that future studies should report numerical measures of both completeness and correctness, use unbiased sample selection to reflect the underlying population, select a gold standard that approximates the true state of the patient, and blinding of the reviewers when a gold standard is administered. We believe our study fulfills most of these requirements.

One reason the electronic system failed to correctly capture some treatment indications was the inability to identify and provide all off-label indications within the electronic system to physicians. While free-text entry is part of the application, the lack of standardization hampers the usability of the data. The creation of a searchable indications list from the treatment indications database should address this problem. To search for drugs, the MOXXI application uses 'auto-completion', where the first three letters entered retrieve a list of all drugs beginning with those letters. This is one of the features of the system identified by the physicians as being important in saving time (47). In the future, the same strategy will be used for treatment indication to capture undocumented off-label indications. These efforts may further increase the PPV of electronic prescribing systems in capturing the correct treatment indications. The study also shows that even with a mandatory requirement for treatment indication documentation, some indications can be missed because of errors in interacting with the computer and an incomplete drug knowledge database.

Another limitation of the study is the exclusion of physicians with less than 2 years of experience in using the electronic prescribing system. Physicians with less experience in electronic prescribing may make more errors than established physicians. This would reduce sensitivity and PPV, at least in the short term as this technology is being adopted.

Governments and health systems are spending billions of dollars to implement electronic health records (376;377). This investment presents a timely opportunity to identify critical elements of health data that can be used to evaluate the safety and effectiveness of drugs, including treatment indications and outcomes (e.g. discontinuation of a drug due to ADEs or ineffectiveness). Treatment indication can be documented at the time of prescribing. This information facilitates the evaluation and dispensing of drugs by the pharmacist and helps educate the patient about the reasons for taking the medication. Our study shows that physicians can document treatment indication with high accuracy at the time of prescribing using an electronic prescribing system. This process can be integrated into their workflow. Data from point-of-care systems can be analyzed in real-time (based on a specified set of rules) and can be used to aid in decision making. The best illustration of this capacity is the implementation of online adjudication systems for drug insurance plans that provide immediate feedback, at the point of purchase on coverage and patient co-pay requirements

(378). Our system has the capacity to collect, in real-time, reasons for discontinuation of drugs due to ADEs. This information can be made available, in real-time, to the prescribing physician as well as other physicians. Broad-scale adoption of electronic documentation of treatment indication nationally and internationally, coupled with information on drug discontinuations, would allow the creation of data in real-time to evaluate the safety and effectiveness of drugs in relation to the treatment indication.

Conclusions

The electronic prescribing system offers a valid method for documenting treatment indication at the time of prescribing. Our results provide strong evidence to support incorporating mandatory recording of treatment indication in integrated electronic prescribing systems to provide a critical piece of information for the evaluation of safety and effectiveness of drugs.

Table 5.1 Characteristics of patients

Characteristics	Value
Age [mean (median)]	58.2 (60)
No. of active drugs [mean (median)]	3.9 (2)
No. of medical problems [mean (median)]	8.3 (9)
Female [n (%)]	210 (62.1)

Table 5.2 Most frequently occurring treatment indications

Treatment indications	Frequency (%)
Hypertension	67 (19.8)
Depression	57 (16.9)
Pain and inflammation	40 (11.8)
Diabetes mellitus	32 (9.5)
Hypercholesterolemia	25 (7.4)
Hypothyroidism	20 (5.9)
Gastro-esophageal reflux	18 (5.3)
Osteoporosis	12 (3.6)
Hormone replacement	11 (3.3)

Table 5.3 Sensitivity and positive predictive value (PPV) of the Medical Office of the XXI century (MOXXI) application in documenting treatment indications.

		Chart review		
		Correct treatment indication	Incorrect treatment indication	Total
Electronic Prescribing system	Indication documented	323	10	333
	Indication not documented	5	TN	TN+5
	Total	328	TN+10	338+TN

Sensitivity (Completeness) = TP/(TP+FN) =

323/(323+5)=98.5%;

PPV (Correctness) = (TP)/(TP+FP) = 323/(323+10) = 97.0%,

Where **FN** = false negatives; **FP** = false positives; **TN** = true negatives; **TP** = true positives

Table 5.4 Study drugs and their off-label treatment indications

Drug	Off-label indications	No. of occurrences
Amitriptyline	Chronic pain	4
Gabapentin	Neurogenic (neuropathic) pain	4
Clonazepam	Restless leg syndrome	2
Amitriptyline	Insomnia	2
Citalopram	Obsessive-compulsive behaviour	2
Clonazepam	Anxiety	2
Atenolol	Anxiety	1
Paroxetine	Alcoholism	1
Risperidone	Alcoholism	1
Bupropion	Alcoholism	1
Desipramine	Attention-deficit syndrome	1
Amiodarone	Angina	1
Quetiapine	Depression	1
Citalopram	Generalized anxiety disorder	1
Hydroxyurea (hydroxycarbamide)	Essential thrombocytopenia	1
Nortriptyline	Migraine	1
Propranolol	Post-traumatic stress disorder	1
Tiotropium	Bronchial asthma	1
Total		**28**

Chapter 6. Drug, patient, and physician characteristics associated with off-label prescribing in primary care

Preamble to manuscript 3

The purpose of this manuscript was to evaluate the prevalence of off-label prescribing, to quantify the strength of evidence for the off-label prescribing, and to determine drug, patient and physician characteristics that influence off-label prescribing in primary care. This manuscript is related to the topic covered in the second section of the background ("Off-label prescribing and use"). The sensitivity and positive predictive value of documentation of treatment indication reported in manuscript two were essential for this study since the measures showed very high completeness and correctness of the data. Investigation of off-label prescribing in adult populations has rarely been done because treatment indication data is not part of typical drug utilization databases, leaving no direct link between drugs and their treatment indications in most EHRs. In the MOXXI EHR, drugs and treatment indications are linked at the time of drug prescribing, creating an unprecedented opportunity to investigate prescription drugs and their use. In addition, the availability of detailed patient and physician data allowed the investigation of the various determinants of off-label prescribing. In addition, manuscript three provides the foundation for manuscript 4 by determining the on- or off-label status of the drug and the strength of evidence for each drug prescription to investigate the outcome of these treatments.

Title Page

Title: Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care

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Abstract

Background: Off-label prescribing may lead to adverse drug events. Little is known about its prevalence and determinants resulting from challenges in documenting treatment indication.

Methods: We used the Medical Office of the XXIst Century (MOXXI) electronic health record network in Quebec, Canada, where documentation of treatment indication is mandatory. One hundred thirteen primary care physicians wrote 253,347 electronic prescriptions for 50,823 patients from January 2005 through December 2009. Each drug indication was classified as on-label or off-label according to the Health Canada drug database. We identified off-label uses lacking strong scientific evidence. Alternating logistic regression was used to estimate the association between off-label use and drug, patient, and physician characteristics.

Results: The prevalence of off-label use was 11.0%; of the off-label prescriptions, 79.0% of the lacked strong scientific evidence. Off-label use was highest for central nervous system drugs (26.3%), including anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%). Drugs with three or four approved indications were associated with less off-label use compared with drugs with one or two approved indications (6.7% vs. 15.7%; adjusted odds ratio [AOR], 0.44; 95% CI, 0.41-0.48). Drugs approved after 1995 were prescribed off-label less often than were drugs approved before 1981 (8.0% vs. 17.0%; AOR, 0.46; 95% CI, 0.42-0.50). Patients with a Charlson Comorbidity Index of one or higher had lower off-label use than did patients with an index of 0 (9.6% vs 11.7%; AOR, 0.94; 95% CI, 0.91-0.97). Physicians with evidence-based orientation were less likely to prescribe off-label (AOR, 0.93; 95% CI, 0.88-0.99), a 7% reduction per 5-points in the evidence section of the Evidence-Practicality-Conformity Scale.

Conclusion: Off-label prescribing is common and varies by drug, patient and physician characteristics. Electronic prescribing should document treatment indication to monitor off-label use.

Introduction

Off-label prescribing, the use of drugs for indications that have not received regulatory approval, is common, occurring with up to 21% of prescribed drugs (18). Although the absence of regulatory approval for a treatment indication does not mean a drug is harmful in that circumstance, off-label use is suspected to be an important determinant of preventable adverse drug events. Indeed, off-label use of fenfluramine-phentermine was shown to cause cardiac valve damage (7;28). When tiagabine, a drug approved to treat partial seizures, was used off-label to treat psychiatric conditions, seizures and status epilepticus occurred (31). More recently, the use of quinine for nocturnal leg cramps, an off-label indication, resulted in serious adverse drug reactions, including thrombocytopenia and gastrointestinal bleeding (379). However, there has not been any systematic investigation of the risks and benefits of off-label use beyond single drugs (256).

In addition, little is known about the factors that contribute to off-label prescribing that may determine systematic differences in treatment outcome. The paucity of knowledge is in part related to the methodologic challenges of measuring off-label use and its effects (26). In most settings, treatment indication is not a required element of prescription. The indication for treatment needs to be inferred by reviewing either health problems documented in the patient's chart or diagnostic codes entered in physician surveys. For off-label use, the reason for treatment is, therefore, difficult to discern (18;33). Inclusion of treatment indications as a required field of an electronic prescription has been proposed as one method of addressing this problem and enhancing pharmacosurveillance (26;33;39;380). To our knowledge, this study is the first to take advantage of the inclusion of treatment indication in an electronic health record (EHR) to evaluate off-label use and assess drug, patient, and physician factors that influence off-label prescribing.

Methods

Context and study population

The Medical Office of the XXIst Century (MOXXI) primary care EHR network research program was used as a source of data (47). There are 113 primary care physicians and 50 823 patients in this research program. Eligible physicians practice in urban centers in Quebec, Canada, work in office-based practice for 3 or more days per week, and are located within 40 km of the research offices. Overall, 410 physicians met these criteria, and 113 physicians (27.6%) consented to participate in this study. On average, participating physicians were 5 years younger than non-participating physicians. All patients who received electronic prescriptions from these physicians and all prescriptions written between January 1, 2005 and December 31, 2009 for drugs used by these patients were evaluated for this study. Ethics approval was granted by the McGill Faculty of Medicine Institutional Review Board.

Three features of the MOXXI EHR permit off-label use to be documented accurately. First, the system requires selection of a treatment indication for each electronic prescription from a menu of on-label and off-label indications (Figure 3.4). Second, therapeutic indications for a specific drug are updated monthly by a commercial vendor through review of drug monographs, compendiums, and published studies (326). Third, unlisted off-label indications can be entered in a free-text field. To enhance the value for clinicians of recording treatment indication, two useful features are provided. First, documented treatment indications are used to populate the patient's problem list. Second, the history of drugs used with each treatment indication is recorded, including drug discontinuations and dosage changes, along with the reason for treatment failures (e.g. hypotension) (339). As a result, the drug-treatment indication data have been shown (340) to be highly accurate, with a positive predictive value of 97% and sensitivity of 98.5%.

Off-label use

Each prescription was classified as on-label or off-label according to the Health Canada drug approval database (333). Indications were considered to be Health Canada approved (i.e., on-label) if they could be matched to the therapeutic indication reported in the drug's package insert as of December 2010, regardless of dosage, frequency, route of administration, duration of treatment, and patients' age range. Any indication that could not be matched to the labeled indication was considered off-label. For each off-label drug indication pair, the

level of evidence supporting the drug's overall efficacy was categorized with the DrugPoints System, which uses the same drug information as DrugDex (both Thomson Reuters). These systems, which are used by Medicare/Medicaid to determine reimbursement for drugs (341), describe the relationship between drug and treatment indication using three dimensions: level of efficacy (effective, favors efficacy, inconclusive, or ineffective), strength of recommendation (for all patients, most patients, specific patients, or not recommended), and strength of evidence (randomized controlled trial [RCT] with consistent results, RCT with inconsistent results, or no RCT). We followed a published algorithm (33), and used these dimensions to determine whether there is strong scientific evidence for the off-label use of a drug for a particular treatment indication. Strong evidence exists when (1) the drug is effective or favors efficacy for a particular treatment indication, (2) the drug is recommended for most or all patients with the treatment indication, and (3) the studies used to evaluate efficacy and the strength of evidence included at least one RCT (33).

Potential risk factors for off-label prescribing

Drug characteristics: We measured *drug class* as a potential risk factor for off-label use because research (18) has shown that medications approved for psychiatric and allergy indications are more likely than other agents to be prescribed off-label. Drugs were classified using the American Hospital Formulary Service (AHFS). *Drug age*, defined as the year the drug was approved for marketing, was included because drugs that have been on the market longer have had a greater opportunity for off-label use. *Drug age* was categorized into 3 groups (before 1981, between 1981 and 1995, and after 1995) because the specific year could not be found for drugs approved before 1981 and 1996 was taken as mid-year between 1981 and 2009. The *number of approved indications for a drug*, defined as a count of Health Canada-approved indications, was included because drugs with fewer approved indications may have a higher likelihood of being prescribed off-label.

Patient characteristics: Age, sex, and co-morbidity (Charlson Comorbidity Index) were assessed because older patients and those with a comorbidity may be less likely to receive off-label prescriptions owing to higher risks of adverse events (268). Pharmacokinetic and pharmacodynamics factors differ between males and females (292), resulting in varied

responses to certain drugs (293), which may increase the chance of receiving prescriptions for off-label drugs (216).

Physician characteristics: We measured 3 physician characteristics. *Years* since *graduation from medical school* was used as a proxy for physicians' knowledge of drugs. Older physicians are more likely to use drug detailers as a source of drug information, and, therefore, may be more likely to prescribe off-label (191;342). *Physician sex* was included because male physicians are more likely to prescribe new drugs than are female physicians (173;343). We hypothesized that physicians who follow evidence-based medicine would be less likely to prescribe off-label. We used the evidence scale from the Evidence-Practicality-Conformity questionnaire (344). This scale predicts clinical guideline compliance and measures the extent to which a physician prefers scientific evidence as the best source of knowledge in clinical decision making (e.g. on-label prescribing) compared with clinical experience or opinion leaders (344;345). High scores in the evidence scale indicate evidence-based orientation.

Statistical analysis

The prevalence of off-label prescriptions was calculated by dividing the number of off-label prescriptions by the total number of prescriptions for a given drug, drug class, and overall. In addition, off-label use was partitioned into off-label with and without strong scientific evidence. The prevalence of off-label use without strong scientific evidence was calculated using off-label prescriptions as a denominator.

To assess determinants of off-label use, a multi-level approach was used, with prescription (drug-indication pair) being the unit of analysis. Drug, patient, and physician characteristics represented the three levels in the analysis and clustering of drugs within each patient and patients within physician was accounted for using alternating logistic regression, a multilevel analytic approach for binary outcomes (346-348). In alternating logistic regression, within-patient and within-physician clustering is described with pair-wise odds ratios (ORs) rather than intra-class correlations. Two outcome variables were evaluated: off-label status (yes/no) and off-label status without strong evidence vs. on-label and off-label status with strong evidence.

Results

A total of 650,237 electronic prescriptions were written between January 2005 and December 2009 and a total of 253,347 unique patient and drug indication combinations were identified once repeated prescriptions were removed, representing 50,823 patients, 113 physicians, and 684 drugs. Overall, 11.0% of drugs were prescribed for an off-label indication and 79.0% of off-label use lacked strong scientific evidence (Table 6.1).

Variation in off-label prescribing was observed among drug classes (Table 6.1). The highest proportion of off-label prescribing occurred with central nervous system drugs (26.3%), anti-infective agents (17.1%), and ear-nose-throat medications (15.2%). Among central nervous system drugs, the highest proportions of off-label use were for anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%) (Figure 6.1). The lowest off-label prescribing was for formulary-restricted drugs (2.9%) and blood and coagulation drugs (1.7%). Scientific support for an off-label use was lowest for anti-neoplastic (0%) and ear-nose-throat (1.6%) drug classes and highest for cardiovascular (58.8%) and dermatologic (65.9%) drug classes.

Specific drugs with the highest off-label use included quinine sulfate (99.5% of prescriptions) followed by gabapentin (99.2%), clonazepam (96.2%), amitriptyline hydrochloride (93.7%), trazodone (92.6%), and betahistine hydrochloride (91.5%) (Table 6.2). Among the top 15 drugs with the highest off-label use, 8 did not meet study criteria for having strong scientific evidence. The lowest prevalence of off-label use was for anti-diabetics (0%-2%), lipid-lowering agents (0%-0.5%), and anti-migraine medications (0%).

Indications that were most likely to be treated with off-label drugs included nocturnal leg pain and benign positional vertigo, for which 100% of the drugs prescribed were off-label (Table 6.3). Neurogenic pain was treated off-label 99.5% of the time with drugs including gabapentin, amitriptyline and topiramate. Other indications with high rates of off-label prescribing included fibromyalgia (67.0%), arrhythmia (60.2%), generalized anxiety disorder (46.5%), and insomnia (43.6%).

Absolute rates of off-label use and off-label use without strong evidence stratified by drug, patient and physician characteristics are reported on Table 6.4. Older drugs (approved before 1996), drugs with one or two approved indications, and the oldest and the sickest patient groups had more scientifically supported off-label use compared with their counterparts. Pairwise ORs for within-patient and within-physician clustering with no covariates were 1.24 (95% CI, 1.21-1.29) and 1.07 (95% CI, 1.04-1.09), respectively, indicating that off-label clustering was greater within patient than within physician.

In a multivariable analysis (Table 6.4), central nervous system drugs were associated with more off-label use than were cardiovascular drugs (26.3% vs. 3.3%; adjusted OR [AOR], 9.91; 95% CI, 9.07-10.84), and formulary-restricted drugs had lower off-label use (2.9%; AOR, 1.01; 95% CI, 0.87-1.16). Drugs with 3 or 4 approved indications had lower off-label use compared with drugs with 1 or 2 approved indications (6.7% vs. 15.7%; AOR, 0.44; 95% CI, 0.41-0.48). In addition, drugs with 5 to 7 and those with 8 or more approved indications had lower off-label use: 9.6% (AOR, 0.62; 95% CI, 0.57-0.67) and 9.7% (AOR, 0.32; 95% CI, 0.28-0.37), respectively. Drugs approved after 1995 had lower off-label use than did drugs approved before 1981(8.0% vs. 17.0%; AOR, 0.46; 95% CI, 0.42-0.50); drugs approved between 1981 and 1996 also had lower off-label use than those approved before 1981 (8.4%; AOR, 0.48; 95% CI, 0.43-0.55). Women received more off-label drugs than men (11.8% vs. 9.7%; AOR, 1.06; 95% CI, 1.03-1.09). Patients with a Charlson Comorbidity Index score of one or higher had lower off-label use than did patients with a Charlson Comorbidity Index score of 0 (9.6% vs. 11.7%; AOR, 0.94; 95% CI, 0.91-0.97). Physicians with higher scores on evidence-based practice were less likely to prescribe off-label. A 5-point increase in the physicians' evidence score on the Evidence-Practicality-Conformity scale decreased the risk of off-label prescribing by 7% (AOR, 0.93; 95% CI, 0.88-0.99). Patient age, physician sex, and physician graduation year were not associated with off-label use.

When the analysis was restricted to off-label prescribing without strong evidence, there were notable differences (Table 6.4). The OR for the central nervous system, anti-infective, ear-nose-throat, and anti-neoplastic drug classes increased by more than 2-fold owing to small percentages of off-label use with strong scientific support in these classes and a large percentage of strong scientific support in the cardiovascular (reference) group. Older drugs

and drugs with one or two approved treatment indications still had the highest risk for off-label use; however the risk was attenuated. Physicians who graduated in the 1980s and those who graduated in the 1990s-2000s prescribed off-label without scientific evidence more frequently than did the 1960-1970 graduates. In addition, the physician evidence-based practice score had a stronger effect on off-label prescribing without scientific evidence, with a 5-point increase in physicians' evidence scale decreasing off-label prescribing without scientific evidence by 10% (AOR, 0.90; 95% CI, 0.85-0.96).

Discussion

To our knowledge, this is the first study to assess off-label prescribing using an EHR platform that explicitly linked treatment indications to prescribed drugs. By using novel, validated drug-indication data collected at the time of prescribing, we were able to address the 2 most important drawbacks in the assessment of off-label prescribing: lack of a link between the prescribed drug and its indication for use and the drug, patient, and physician characteristics associated with off-label prescribing. Moreover, it was possible to identify treatment indications associated with a high prevalence of off-label drug use that would benefit from new drug development or RCTs.

In this study, we found that 11% of drugs were prescribed off-label and that, among these, 79% lacked strong scientific evidence. The magnitude of off-label use was less than in the 2001 US study (18). The difference in off-label use can be explained by the difference in the drugs and the populations examined. Our study included all drugs prescribed to an adult population (predominantly older); while the US study included 160 drugs prescribed for adults and children. However, the proportion of off-label use not supported by strong scientific evidence was comparable. Both studies found that psychiatric and anti-convulsant drugs had the highest off-label use. In our study, formulary-restricted drugs had lower off-label use, probably because physicians had to justify the use of the drug for the specific indication or had to try other drugs first, which is known to affect prescribing (381). A physician's lack of knowledge about drugs (164) and the scarcity of approved or efficacious drugs may be reasons for some of the off-label prescribing (244;382).

The reasons for the association of older drugs with off-label use include that these medications have been on the market longer, thereby creating the opportunity for experimentation and discovery of new uses by clinicians (383). In addition, these drugs are off-patent, with no sponsor to perform RCTs or apply for the inclusion of new indications to the label (159). Contrary to a previous study (18), we observed that drugs with fewer approved indications had higher rates of off-label use. However, some single indication drugs, such as anti-migraine and anti-diabetic agents had the lowest level of off-label prescribing (18), implying that their use is too specific to treat any other condition.

Sicker patients were less likely to receive off-label drugs, which may be the result of their poor health creating less room to "experiment" with a drug. This trend has also been observed in children (384). In our study, women received more off-label prescriptions than men because women were more likely to be treated for problems such as anxiety, nocturnal leg pain, and insomnia, conditions for which off-label prescribing is common.

Physicians with evidence-based orientation were less likely to prescribe off-label, and this effect was increased for drugs prescribed off-label without strong scientific evidence. This observation implies that physicians who give emphasis to evidence-based medicine base their treatment decisions not only on data from drug regulatory bodies but also using the overall evidence available in sources including peer-reviewed publications, clinical guidelines and recommendations from professional societies. Currently, there is an effort to educate physicians on the level of evidence and appropriate off-label uses (251;385;386) with the aim of linking off-label use with rigorous outcome evaluation, with the physician being an active participant in evidence development. Connecting drugs with their treatment indications and providing evidence to support off-label use at the time of prescribing would be one way of addressing scientifically unsupported off-label use.

This study has several limitations. First, the definition of *off-label* was conservative, since it did not include dosage, frequency, route of administration, duration of treatment, and patients' age range, which, if considered, would increase the prevalence of off-label prescribing. Second, some off-label use may be explained by co-morbidities; however, the potential for misclassification was low owing to the explicit linking of drugs with their indications. Third,

the compendium used to evaluate level of evidence for off-label use has limitations. The methods used to classify evidence are not transparent and the evidence is not necessarily up-to-date; however, this compendium documents a comprehensive list of off-label indications with their level of evidence better than other compendia (33;341). Fourth, the physicians in the study were younger and were willing to use an EHR; this may limit the generalizability of the findings to other physician groups. Fifth, because we did not capture non-pharmacologic treatments and their indications, the findings are conditional on having a drug prescribed for an indication. We also could not directly compare the off-label rates using an EHR and previous methods because of the unavailability of nationally representative physician survey data in Canada.

Countries are spending billions of dollars to implement EHRs (376;377). In the United States, objectives for "meaningful use" of EHRs were defined to achieve improvement in health care quality (387). Maintaining an active medication and problem (diagnosis) list were among the core objectives identified that are essential to create a medical record. These 2 tasks are seamlessly integrated in the MOXXI electronic prescribing system, which generates the medication and problem lists in real time. Linking a prescribed drug with an indication could be a meaningful use objective, and vendors could easily incorporate this feature into EHR systems. Moreover, reasons for discontinuation of drugs (e.g. adverse drug reactions and ineffective treatments) can be linked to treatment indications, creating a novel pharmacosurveillance tool to evaluate the safety and effectiveness of drugs (339), thereby advancing meaningful use to meaningful benefit (388). In addition, drug regulatory bodies may use the data (drug indication and reason for discontinuation) to facilitate the post-marketing surveillance of both on-label and off-label use of drugs at the time they enter the market.

Conclusions

Our findings indicate that off-label prescribing is common in primary care and varies by drug class, the number of approved indications for the drug, the age of the drug, patients' sex, and physicians' attitude towards evidence-based medicine. Electronic health records can be used

to document treatment indication at the time of prescribing and may pave the way for enhanced post-marketing evaluation of drugs if linked to treatment outcomes.

Table 6.1 Distribution of off-label use by AHFS therapeutic class and the level of scientific support.

Drug AHFS Class	Number prescriptions	Off-label use		Proportion of off-label use by degree of scientific evidence,[a b]	
		N	%	With strong evidence (%)	Without strong evidence (%)
Central nervous system	58914	15491	26.3	18.2	81.8
Ear-nose-throat	10622	1613	15.2	1.6	98.4
Gastro-intestinal	14237	1770	12.4	15.1	84.9
Hormone and synthetics	34868	1366	3.9	34.5	65.5
Skin and mucous membrane	15815	760	4.8	65.9	34.1
Formulary restricted	11174	327	2.9	48.6	51.4
Anti-histamine	348	21	6.0	19.0	81.0
Anti-infective	21000	3599	17.1	4.6	95.4
Anti-neoplastic	234	28	12.0	0	100.0
Autonomic	13854	540	3.9	12.2	87.8
Blood and coagulation	1328	23	1.7	0.0	100.0
Cardiovascular	70953	2313	3.3	58.8	41.2
Total	253347	27851	11.0	21.0	79.0

[a]The proportion of off-label use according to scientific evidence was calculated using the number of off-label prescriptions as a denominator. For example, 18.2% of the 15491 off-label central nervous system prescriptions had strong scientific evidence for their use. Of the 27851 off-label prescriptions, 21% had strong scientific evidence.

[b]DrugPoints® synthesizes efficacy data, strength of evidence and the level of recommendation to categorize degree of existing scientific evidence for each drug-indication (off-label) pair. A published algorithm (33) was used to categorize whether strong scientific evidence exists depending on the Drugpoints® classification.

Table 6.2 Off-label use by drug and the degree of scientific evidence

Drug name	Number prescriptions	Off-label (%)	With strong evidence (%)*	Without strongevidence (%)*
Quinine sulfate	953	99.5	0.0	100.0
Gabapentin	840	99.2	4.0	96.0
Clonazepam	2370	96.2	1.1	98.9
Amitriptyline	1670	93.7	45.4	54.6
Trazodone	1700	92.6	0.0	100.0
Betahistine	715	91.5	0.0	100.0
Oxazepam	2132	72.0	98.1	1.9
Quetiapine	983	66.7	0.0	100.0
Azithromycin	2155	65.7	3.7	96.3
Olanzapine	478	54.2	0.0	100.0
Diclofenac+Misoprostol	899	53.1	18.2	81.8
Risperidone	480	43.8	0.0	100.0
Celecoxib	3987	42.4	0.0	100.0
Bisoprolol	1661	40.4	97.9	2.1
Citalopram	2973	35.6	0.0	100.0

*The two percentages total 100%. For example, only 4.0% of the 99.2% of gabapentin off-label use had strong scientific evidence; the rest (96.0%) had no strong scientific evidence.

Table 6.3 Top 10 clinical indications treated with off-label drugs and their most frequent off-label drugs[a]

Treatment indications	Number Prescriptions	Off-label N (%)	Most common off-label drug (%)	Second most common off-label drug (%)	Third most common off-label drug (%)
Benign positional vertigo[b]	653	653 (100.0)	Betahistine (100.0)	- - -	- - -
Nocturnal leg pain[b]	948	948 (100.0)	Quinine (100.0)	- - -	- - -
Neurogenic pain	1153	1147 (99.5)	Gabapentin (51.5)	Amitriptyline (15.5)	Topiramate (7.8)
Chronic pain	251	213 (84.9)	Amitriptyline (90.1)	Gabapentin (0.9)	Nabilone (0.5)
Fibromyalgia	816	547 (67.0)	Cyclobenzaprine (74.0)	Gabapentin (11.0)	Venlafaxine (6.0)
Arrhythmia	752	453 (60.2)	Metoprolol (37.1)	Atenolol (34.3)	Nadolol (18.7)
Generalized anxiety disorder	3275	1522 (46.5)	Citalopram (54.7)	Clonazepam (13.7)	Sertraline (12.6)
Insomnia	10392	4535 (43.6)	Oxazepam (33.2)	Trazodone (29.9)	Clonazepam (11.7)
Bipolar disorder	643	177 (27.5)	Lamotrigine (74.0)	Topiramate (13.6)	Gabapentin (11.3)
Diabetic neuropathy	338	68(20.1)	Gabapentin (89.7)	Pentoxifylline (5.9)	Paroxetine (4.4)

[a]The drugs, treatment indications and off-label status are based on the Health Canada drug database.(333) Some drugs included in this table may not be approved in other countries. Some off-label indications may be listed as an approved indication in other countries. For example, gabapentin was approved for only one indication (adjuvant therapy for partial seizure) in Canada and the United states; postherpetic neuralgia was added to the label in 2004 in the United States.

[b]Treatment indications with no approved drugs.

Table 6.4 Proportion of off-label prescribing and multivariate analysis with two outcomes: Off-label and off-label without strong scientific evidence

Variable	Off-label (%)	AOR (95% C.I)	Off-label without scientific Evidence (%)	AOR (95% CI)
Drug age				
Before 1981	17.0	1 (Reference)	13.0	1 (Reference)
1981- 1995	8.4	0.48 (0.43, 0.55)	6.0	0.45 (0.39, 0.52)
1996 - 2009	8.0	0.46 (0.42, 0.50)	7.4	0.67 (0.61, 0.73)
Drug Class				
Cardiovascular	3.3	1 (Reference)	1.3	1 (Reference)
CNS	26.3	9.91 (9.07, 10.84)	21.6	19.42 (17.38, 21.69)
Anti-infective	17.1	9.53 (8.09, 11.23)	16.6	22.54 (18.82, 26.99)
ENT	15.2	5.23 (4.63, 5.91)	15.1	14.10(12.14, 16.38)
Gastro-intestinal	12.4	8.77 (7.22, 10.66)	10.6	14.97 (12.02, 18.65)
Anti-neoplastic	12.0	3.29 (2.17, 5.00)	11.9	9.50 (6.21, 14.54)
Anti-histamine	6.0	0.75 (0.43, 1.29)	4.9	1.97 (1.06, 3.66)
Skin and mucous membrane	4.8	1.57 (1.37, 1.79)	1.7	1.32 (1.06, 1.65)
Hormone and synthetics	3.9	1.21 (1.05, 1.39)	2.6	2.00 (1.71, 2.34)
Autonomic	3.9	1.11 (0.94, 1.31)	3.6	2.50 (2.10, 2.98)
Formulary-restricted	2.9	1.01 (0.87, 1.16)	1.5	1.15 (0.94, 1.42)
Blood and coagulation	1.7	0.65 (0.41, 1.01)	1.7	1.64 (1.05, 2.55)
Approved indication count				
1 - 2	15.7	1 (Reference)	11.2	1 (Reference)
3 - 4	6.7	0.44 (0.41, 0.48)	5.7	0.62 (0.57, 0.68)
5 - 7	9.6	0.62 (0.57, 0.67)	7.8	0.83 (0.76, 0.91)
8 and above	9.7	0.32 (0.28, 0.37)	8.7	0.44 (0.37, 0.51)

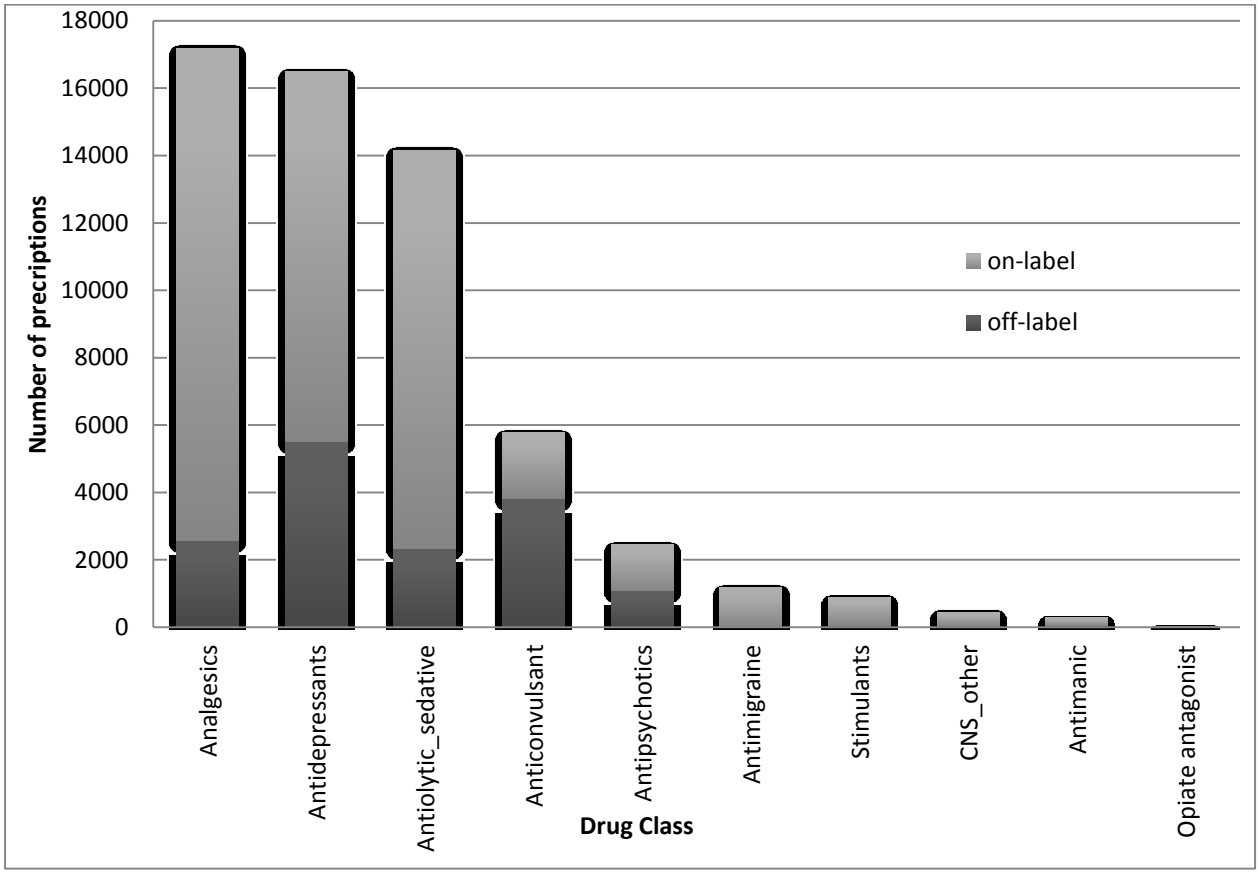
Table 6.4 (continued). Proportion of off-label prescribing and multivariate analysis with two outcomes: Off-label and off-label without strong scientific evidence

Variable	Off-label (%)	OR (95% C.I)	Off-label without strong scientific evidence (%)	OR (95% CI)
Patient age, y				
<48.5 years	13.6	1 (Reference)	11.5	1 (Reference)
48.6 - 60.5 years	12.4	1.04 (1.00, 1.09)	10.2	1.03 (0.98, 1.08)
60.6 - 71.5 years	10.3	1.04 (0.98, 1.09)	8.1	1.02 (0.96, 1.08)
>71.5 years	9.2	1.01 (0.96, 1.07)	6.8	0.95 (0.90, 1.01)
Patient sex				
Male	9.7	1 (Reference)	7.6	1 (Reference)
Female	11.8	1.06 (1.03, 1.09)	9.4	1.05 (1.02, 1.09)
Charlson Comorbidity Index				
0	11.7	1 (Reference)	9.4	1.00 Reference
≥1	9.6	0.94 (0.91, 0.97)	7.4	0.95 (0.92, 0.99)
Physician graduation year				
1960-1979	10.6	1 (Reference)	8.3	1 (Reference)
1980-1989	11.2	1.08 (1.00, 1.16)	9.0	1.10 (1.01, 1.19)
1990-2000s	11.3	1.08 (0.99, 1.18)	9.1	1.11 (1.01, 1.21)
Physician sex				
Male	11.2	1 (Reference)	8.9	1 (Reference)
Female	10.7	0.99 (0.93, 1.05)	8.5	0.98 (0.92, 1.05)
Physician evidence scale, mean, (SD); (range)[a]	21.2 (2.5); (14-28)	0.93 (0.88, 0.99)		0.90 (0.85, 0.96)

Abbreviations: AOR, adjusted odds ratio; CNS, central nervous system; ENT, ear-nose-throat;

[a] Indicates the physician's attitude toward evidence-based medicine. The AOR is per 5-unit increase in the evidence scale in Evidence-Practicality-Conformity instrument, which is a psychometric instrument developed by the University of Michigan to study determinants of the adoption of evidence-based practice. The objective of the instrument is to capture physicians' variability in (1) judging the credibility of a source of information (evidence), (2) the emphasis given to practical concerns (practicality), and (3) the readiness to differ from the group norm in practice (conformity). The instrument underwent the various validation stages using more than 1200 physicians. The internal consistencies, measured by Cronbach α, were 0.79 for the evidence scale, 0.74 for the conformity scale and 0.68 for the practicality scale. (344) It was shown that physician characteristics measured by the instrument affected responses to clinical guideline implementation strategies. (345)

Figure 6.1 Frequency distribution of central nervous system (CNS) drugs by drug approval status (on- and off-label).



Chapter 7. Off-label use is a predictor of adverse drug events in adults

Preamble to manuscript 4

The purpose of this manuscript was to determine the association between off-label use and adverse drug events. This manuscript builds on the three earlier manuscripts: it uses the measure of treatment change and indication developed in manuscript one and two, and it uses the on-label and off-label status of the prescriptions and the strength of evidence for the off-label use from manuscript three. The background discusses the challenges of present-day pharmacosurveillance in monitoring off-label prescribing in relation to this manuscript. For the first time, the effect of off-label use in adult populations was systematically investigated using an EHR which was geared to document important signposts of drug treatment in a patient: the reason for drug initiation, and the reason for drug change or discontinuation. Additionally, important previously identified determinants of ADEs were investigated.

Title Page

Title: Off-Label Use is a Predictor of Adverse Drug Events in Adults

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Abstract

Background: Off-label use has been identified as an important contributor to preventable adverse drug events (ADE) in children. Despite concerns for adverse outcomes, there has been no systematic investigation of the effects of off-label use in adult populations.

Methods: The MOXXI electronic health record (EHR), which supports accurate documentation of treatment indications and treatment outcomes, was used to assemble a cohort of 46,294 patients who received 153,144 incident drugs between January 2005 and December 2009. Person-time was accrued until the drug was discontinued or the end of follow-up (December 2010). Outcome: Adverse drug events (ADE) were defined as drug discontinuations made by physicians due to "adverse drug reactions" and "allergic reactions". Exposure: treatment indication recorded for each drug was classified as on- or off-label using Health Canada drug database and off-label use was divided into use with and without strong scientific evidence. Other covariates include drug class, drug age, patient age, sex, comorbidity, number of drugs and continuity of care (COC) index. Statistical analysis: Multivariate marginal Cox regression for clustered data where the unit of analysis was drug.

Results: There were 3,499 ADEs with an incident rate (IR) of 13.3 per 10,000 person-months. The off-label ADE rate (19.8/10,000 person-months) was higher than on-label uses (12.5 per 10,000 person-months) [HR, 1.43 (95% CI, 1.29, 1.59)]. When off-label use was stratified according to scientific evidence, off-label uses which lack scientific evidence had a higher ADE rate (21.8 per 10,000 person-months compared to on-label use [HR, 1.53 (95% CI, 1.37, 1.72)]. Other factors associated with an increased risk of ADEs included: patients who had received ≥8 drugs had increased risk of ADE than patients with 1–2 drugs [IR: 19.1 vs. 4.4; HR, 5.77 (95% CI, 4.77, 6.97)]; anti-infective drugs compared to gastrointestinal drugs [HR, 6.08 (4.39, 8.43)], patients in the bottom quartile for age (18 – 47.5 years) had higher risk of ADE compared to the three older quartiles. Women had higher risk of ADE than men [HR, 1.12 (95% CI, 1.02, 1.24)]. Drugs approved after 1981 had greater risk of ADE than drugs approved before 1981. A one unit increase in COC index increased the ADE detection by 20% [HR, 1.20, (95% CI, 1.13, 1.27)].

Conclusion: Off-label use is a determinant of adverse drug events. Future electronic health records should be designed to enable post-market surveillance of treatment indications and treatment outcomes to monitor the safety of on- and off-label uses of drugs.

Introduction

Off-label prescribing is common (18;389) and has been identified as a potentially important contributor to preventable adverse drug events (ADE). Significant deleterious effects can occur with off-label use of some drugs such as cardiac valve damage with fen-phen (7;28), status epilepticus with tiagabine(31), thrombocytopenia with quinine (29;379), stroke and invasive breast cancer with hormone replacement therapy (237) and recombinant factor VIIa and increased thromboembolic events (255-257). Moreover, studies in pediatric populations, where drugs are often used without sufficient scientific investigation or regulatory oversight, have shown that off-label uses increase the risk of ADE (21-25).

Despite concerns for adverse outcomes, there has been no systematic investigation of the effects of off-label use in adult populations in real world situation. The paucity of knowledge is in part related to the methodological challenges of measuring off-label use and its effects; specifically the lack of link between prescribed drugs and their indication for use (26;27). Recently, treatment indication, reasons for discontinuation orders and the nature of the adverse drug event, when present have been experimentally developed and validated (339;340) as required fields in an electronic prescription. These new features provided the first opportunity to systematically monitor and evaluate off-label use and the occurrence of adverse drug events. This study took advantage of the use of this new generation of software in a network of primary care practices to systematically evaluate the effect of off-label use on ADEs.

Methods

Context

The study was conducted in Quebec, Canada, a province with 8.5 million residents where the provincial insurance agency provides health insurance for all provincial residents. In 2003, MOXXI, an experimental community-based clinical information system, linked the beneficiary, medical billing and pharmacy claim data into electronic health record system to create longitudinal health histories for each patient (323;390). These data have been validated and are frequently used for health services and epidemiological research (71;72;391;392).

There are 113 primary care physicians in MOXXI research program and these physicians work in office-based practice for three or more days per week, and are located within 40 km of the research offices located in two Quebec urban centers.

In the MOXXI electronic health record, there is a mandatory requirement to document the treatment indication with each new electronic prescription, the reasons for dose changes and drug discontinuation orders, and associated ADE detected by the physician. Structured menus and optional text entry are used to facilitate documentation (Figures 3.1, 3.2, 3.3 and 3.4). To support clinical decision-making, treatment indications automatically populate the patient's problem list, as well as prior treatment and reasons for discontinuations (e.g. ADE, hypotension) that are listed under each indication. ADEs are documented using a pre-populated drug specific ADEs list, mapped to Medical Dictionary for Regulatory Activities (MedDRA) classification. In addition, physicians can also search from the global list of ADE or can text-in a specific ADE description.

Design and Study Population

To evaluate the association between off-label use and adverse drug events, a prospective cohort of 46,294 patients prescribed new (incident) medication was assembled between January 1 2005 and December 30 2009. A drug prescription was considered incident if it had not been prescribed or dispensed in the past 12 months. Patients were followed from the date of the prescription to the date the drug was discontinued or the end of follow-up (December 30 2010).

Adverse Drug Event (ADE)

ADEs were defined as drug discontinuations made by physicians due to "*adverse drug reaction*" or "*allergic reaction*". Prior evaluation of the validity of these data found a concordance of electronic documentation of ADE with the medical chart of 85.7% (339). ADEs documented in the MOXXI system were classified according MedDRA which includes System Organ Classes (SOC) and Preferred terms (PT). SOCs represent the highest hierarchy that provides the broadest concept and PT is a distinct descriptor of sign, symptom, diagnosis, investigation or surgical or medical procedure.

Potential Risk Factors for adverse drug events

Off-label use

The indication recorded for each prescription was classified as on-label or off-label use according to the Health Canada drug approval database (333). Compared with medical chart, the sensitivity (completeness) and the positive predictive value (correctness) of electronic treatment indication documentation were 98.5% and 97%, respectively (340). Indications were considered Health Canada approved or on-label if they could be matched to the therapeutic indication reported in the drug's package insert as of December 2010. Any indication that could not be matched to the labeled indication was considered off-label. For each off-label drug-indication pair, the level of evidence supporting the drug's overall efficacy was categorized using the DrugPoints® System (Thomson Reuters). Strong evidence exists when : i) the drug is effective or favors efficacy for the off-label treatment indication ii) the drug is recommended for at least most patients with the off-label treatment indication, and iii) the studies used to evaluate efficacy and the strength of evidence include at least one RCT (33;389). Accordingly, two variables were created: 1) on- or off-label in accordance with Health Canada approval status, 2) on-label, off-label with strong scientific evidence and off-label without strong scientific evidence.

Drug characteristics: We measured *drug class* as a potential risk factor for ADE as prior research has shown that central nervous system, cardiovascular and anti-infective classes were more often implicated in ADEs (273;278;291;305). Drugs were classified using the American Hospital Formulary Classification (AHFS) system. *Drug age*, defined as the year the drug was approved for marketing, was included as ADEs of recently approved drugs were more likely to be reported than older drugs (306;307). Drug age was categorized into three groups (before 1980; between 1980 and 1996; and after 1996 or recently approved drugs).

Patient characteristics: We included age and measures of comorbidity (Charlson comorbidity index) as older patients (268-272) and those with more comorbidity (278;283;284;286) may exhibit higher risks of ADE. Patient sex was included because higher rates of ADE were reported for females than males (279;281;297;349). *Number of drugs* the patient is taking was included since it was shown to be the most important risk factor for

ADE (21;272;274;278-284). *Continuity of care* (COC) index was included to correct for possible surveillance bias in the opportunity to detect ADEs as patients with better continuity have fewer emergent visits (300;350) possibly because both ADEs and disease exacerbations are more likely to be detected and averted by the primary physician responsible for care. COC index was defined as the ratio of number of a patient's visits to the primary care physician to the square root of the total outpatient visits a patient had and it was calculated using the medical services claims (351).

Statistical Analyses

Incidence rates of drug discontinuations due to ADE were calculated by dividing the number of incident cases by the number of person-months of follow-up, overall and by exposure classification. Person-months were calculated per drug for specific patient starting from the first day of prescription up to the drugs discontinuation/end of treatment or end of the study (December 30, 2010). The hazard ratio (HR) was calculated by dividing the incidence rate in one category by the incidence rate in the reference category. The unit of analysis was drug; and drugs were nested within patients. The marginal Cox model for clustered data was employed with robust sandwich covariance estimate to account for the intra-cluster dependence for both univariate and multivariate analyses and to construct 95% confidence intervals (352;353). The two off-label variable indicators were included in the Cox model one at a time. Proportionality assumptions were tested by covariate-time interaction terms and analyzing Schoenfeld and Martingale residuals and the survival curves (354). As a sensitivity analyses and for comparison purpose a marginal Poisson regression model was also employed.

Results

There were a total of 46,294 patients who received 153,144 incident prescriptions from 2005 to 2009. The person-time of follow-up ranged from 1 day to close to 6 years (median, 386 days; mean, 530). Patients were on average 58.1 years old, predominantly female (60.8%), 24.7% had a Charlson comorbidity index of ≥1, and 41.9% used more than 4 drugs during the study period.(Table 7.1) Central nervous system and cardiovascular drugs constituted 25.1% and 22.8%, respectively. Almost half of the prescribed drugs (46.4%) were approved

for the Canadian market before 1981 while 28.8% of the drugs were approved after 1995. Mean COC index was 1.08 (SD, 0.64). According to Health Canada drug approval status, 11.8% of the prescriptions were off-label among which 81.4% (or 9.6%) lacked strong scientific evidence for their use.

There were 3,499 drug treatments discontinued by physicians due to ADEs, with an incidence rate (IR) of 13.3 per 10,000 person-months (Table 7.2). The ADE rate for on-label uses was lower (12.5 per 10,000 person-months) than for off-label use (19.8 per 10,000 person-months), an increase in the risk of ADE of 43% with off-label use (HR: 1.43 95% CI, 1.29-1.59). When off-label use was stratified to off-label use with and without strong scientific evidence, the ADE rates were 13.4 and 21.8 per 10,000 person-months, respectively. Compared to on-label use, the HRs for off-label use with and without strong scientific evidence were 1.11 (95% CI, 0.88-1.39) and 1.53 (95% CI, 1.37, 1.72), respectively. Proportionality assumptions for the hazards were not violated. (Figure 7.1, 7.2 and Appendix A.1-5)

Anti-infectives had the highest ADE rate (72.4 per 10,000 person-months), a 6-fold increase in risk of ADE compared to gastrointestinal drugs [HR, 6.08 (95% CI, 4.39, 8.43)]. Central nervous system and cardiovascular drugs had ADE rates of 18.1 and 15.9 per 10,000 person-months, respectively. Drugs approved after 1995 had ADE rates that were 51% higher than drugs approved before 1981 [HR, 1.51 (95% CI, 1.36, 1.68)] and the same is true for drugs approved between 1981 and 1995 [HR, 1.59 (95% CI, 1.42, 1.77)].

Dose-response relationships were identified between the number of drugs the patient used and the risk of ADE. Patients who used ≥ 8 drugs had 5.8 fold increased risk of ADE compared to patients with 1-2 drugs [HR, 5.77 (95% CI, 4.77, 6.97)] with ADE rates of 19.1 and 4.4 per 10,000, respectively. After adjusting for the number of medications, patients in the bottom quartile for age (18 – 47.5 years) had a higher risk of ADEs compared to the three older quartiles. Females also had higher risk of ADEs than males (14.3 and 11.7 per 10,000, respectively [HR, 1.12 (95% CI, 1.02, 1.24)]). After adjusting for other patient characteristics, the patients with a Charlson Comorbidity Index of one or higher had the same risk of ADE as did patients with an index of 0 [HR, 0.91 (95% CI, 0.83, 1.00)]. COC

index was an important determinant of ADE detection, with a 20% increase in ADE rate with one unit increase in COC index [HR, 1.20 (95% CI, 1.13, 1.27)].

ADEs related to the gastrointestinal, nervous, respiratory and musculoskeletal SOC were most frequently documented accounting from 22% to 8% of the total ADEs (Table 7.3). Selected examples of ADEs associated with the most frequent off-label used drugs include: akathisia resulting from the use of gabapentin for neurogenic pain; agitation associated with the use of amitriptyline for migraine; hallucinations from the use of trazodone for insomnia; QT interval prolongation from quetiapine used for depression; and weight gain from the use of olanzapine for depression.

Discussion

This is the first study to systematically evaluate the association between off-label use and the risk of ADEs in an adult population. It is also the first to use electronically documented and chart-review validated treatment indications and treatment outcomes (e.g. ADE) to measure treatment indication and ADE occurrence (339;340;389).

We found off-label use was an independent risk factor for ADEs after adjusting for important patient and drug characteristics. Several studies in children have shown that off-label use increased the risk of ADE (21-25). And, our findings that off-label use increases the risk of ADE is not surprising since the drugs used for off-label treatment indications do not undergo the same scrutiny of their safety, dose range, contraindications, and disease-drug interactions as on-label uses. Moreover, off-label uses with strong scientific evidence had risk of discontinuation due to ADEs closer to on-label uses, implying that these drug uses share similar risk profile with the on-label uses. The high risk of ADE for off-label uses implies that there is an inherent distinction between off-label uses with and without strong scientific evidence in terms of their safety, in addition to the effectiveness difference.

As the findings pointed out, four in five off-label prescriptions have little or no scientific evidence and that these prescriptions led to more adverse drug events. This diverse spectrum of off-label use shows that physicians and physician organizations need to recognize the

diversity as well as the lack of scientific evidence for most off-label drug use. We cannot explain every off-label prescription as 'clinically plausible' or their being a 'lack of an alternative drug' or simply to 'patient complexity'. Lack of knowledge of approved treatment indication (164) was demonstrated to be one factor for off-label prescribing. The vast amount of drug information (393) also contributes to off-label prescribing. We need to acknowledge that the lack of knowledge about drugs and the difficulty of keeping up with the ever-changing drug information are affecting how well patients are treated. Using computerized decision support systems, we could fill the knowledge gap by supplying drug approval status and the degree of scientific evidence at the point-of-care. In addition, post-marketing studies should also document treatment indications and treatment outcomes so that drugs can be evaluated according to their use.

Studies (21;272;274;278-284) have shown that the number of drugs used by a patient strongly influences the risk of ADE due to increased risk of inappropriate prescribing (394), drug-drug interaction (395), and drug-disease interaction (396). A concerted effort is needed to decrease drugs to a minimum possible through interventions such as medication reviews (397) that have been recently instituted and funded in many jurisdictions as new pharmacy services that could address these challenges. Other interventions include use of computerized alerts to decrease potential inappropriate prescribing including drug-drug and drug-disease interactions (398;399).

Similar to other studies, we found the rates of ADE were significantly higher in anti-infective, cardiovascular and central nervous system drug classes (273;278;291;305). The rapidly evolving field of pharmacogenomics may play a role in identifying subsets of the population susceptible to the effect of these drugs and prevent adverse drug events as shown in treatment of HIV (400).

Younger and female patients also exhibited high risk of ADE than older and male patients, respectively. We found the same age effect that was reported from the French pharmacovigilance database (285) where the oldest age group had a higher crude rate of ADE but after ADE rate was adjusted by drug consumption, the age groups from 20-49 years had the highest ADE rate. A prescription event monitoring study with more than half a

million patients in the UK reported a similar age trend (267). Higher risk of ADE was reported for females in our study even after accounting for continuity of care index to mitigate the effect of high consultation rates in females. We also identified that patients who had higher COC index had high risk of ADE; possibly due to surveillance detection biases with the opportunity to identifying ADE in their earlier stage. Monitoring patients in the community with a nurse or an interactive voice response system to detect drug related problems (401) and relaying this information to a community pharmacist or the treating physician would be one option of detecting and ameliorating ADEs.

The study has several limitations. First, the ADE identification depends on physicians and patients and physicians are known to miss medication-related symptoms and patients may not also inform their physicians about all of their symptoms (43). Second, ADEs of patients with comorbidities may not be as easily ascribed to the drug (versus concurrent disease) and may not be identified. Third, patients with severe ADEs may visit hospitals and other physicians and the ADEs might not be recorded in the EHR. All these limitations might have resulted in underestimation of ADE incidence. However the underestimation of ADE rates will likely affect both on-label as well as off-label uses equivalently, and thus not bias the association between drug approval status and ADE.

In this study, we showed that an EHR system tailored to document two important variables for the study of drugs and their effects – the reason for drug treatment (treatment indication) and the reason for treatment discontinuation could be used in post-market surveillance of the risk of off-label use. A system like this has been envisioned by many researchers and policy-makers (39;44;45;393) to supplement current approaches to the post-marketing surveillance of drugs. This system will tackle fundamental problems in post-marketing surveillance of drugs, namely, the lack of link between prescribed drugs and their indication for use and under-reporting of ADEs by creating an electronic link between prescribed drug – indication – treatment outcome including ADEs, ineffectiveness, effectiveness and other outcomes.

Conclusion

Our findings indicate that off-label use in general and off-label use without storing scientific evidence in particular are risk factors of ADE. Patients who received more drugs, women and drugs approved after the 1981 were associated with higher adverse drug events. Future EHRs should be designed to enable post-market surveillance of treatment indications and treatment outcomes to monitor the safety of on- and off-label uses of drugs.

Table 7.1 Drug and patient characteristics

Drug characteristics	N	%
On- and off-label and strong scientific status		
On-label	135046	88.2
Off-label	18098	11.8
Off-label with strong evidence	3440	2.2
Off-label without strong evidence	14658	9.6
AHFS Class		
Gastrointestinal	7811	5.1
Central nervous system	38409	25.1
Ear-Nose-Throat	7553	4.9
Hormone and synthetics	20667	13.5
Formulary-restricted	5166	3.4
Anti-infectives	17178	11.2
Autonomic	8089	5.3
Cardiovascular	34889	22.8
Others*	13382	8.7
Drug age		
Before 1981	297	46.4
1981- 1995	159	24.8
1996 - 2009	184	28.8
Patient characteristics	**N**	**%**
Age category		
18 - 47.5 years	12142	26.2
47.6 - 59.5 years	12130	26.2
59.6 - 70.5 years	11185	24.2
> 70.5 years	10837	23.4
Sex		
Males	18148	39.2
Females	28146	60.8
Charlson Index		
0	34877	75.3
≥ 1	11417	24.7
Number of drugs		
1 - 2 drugs	15900	34.4
3 - 4 drugs	11026	23.8
5 - 7 drugs	10261	22.2
≥ 8 drugs	9107	19.7
Continuity of care index	**Mean (SD)**	**IQR, median**
	1.09 (0.63)	0.88; 1.00

Abbreviations: IQR, interquartile range; SD, standard deviation
* - antihistamines, blood and coagulation, anti-neoplastics

Table 7.2 Association between adverse drug events and drug and patient characteristics

	Number of ADR	Person-months in 10,000	Rate per 10,000 person-months*	Univariate Cox	Multivariate Cox
On- and off label					
On-label	2979	237.5	12.5	Ref.	Ref.
Off-label	520	26.2	19.8	1.48 (1.35, 1.64)	1.43 (1.29, 1.59)
Off-label and scientific evidence					
On-label	2979	237.5	12.5	Ref.	Ref.
Off-label with strong evidence	82	6.1	13.4	1.05 (0.84, 1.30)	1.11 (0.88, 1.39)
Off-label without strong evidence	438	20.2	21.8	1.62 (1.46, 1.80)	1.53 (1.37, 1.72)
AHFS Class					
Gastrointestinal	98	16.0	6.1	Ref.	Ref.
Central nervous system	1096	60.7	18.1	2.81 (2.27, 3.49)	2.97 (2.39, 3.68)
Ear-Nose-Throat	32	11.6	2.8	0.42 (0.28, 0.66)	0.43 (0.28, 0.66)
Hormone and synthetics	550	43.2	12.7	2.07 (1.64, 2.59)	2.55 (2.03, 3.20)
Formulary-restricted	114	11.8	9.7	1.66 (1.26, 2.19)	1.90 (1.44, 2.51)
Anti-infectives	87	1.2	72.4	5.61 (4.08, 7.72)	6.08 (4.39, 8.43)
Autonomic	141	16.8	8.4	1.39 (0.95, 2.02)	1.64 (1.11, 2.43)
Cardiovascular	1360	85.7	15.9	2.73 (2.21, 3.37)	3.40 (2.75, 4.21)
Others*	21	16.7	1.3	0.18 (0.11, 0.29)	0.22 (0.14, 0.36)
Drug age					
Before 1981	756	75.3	10.0	Ref.	Ref.
1981- 1995	1145	79.1	14.5	1.49 (1.34, 1.64)	1.59 (1.42, 1.77)
1996 - 2009	1598	109.3	14.6	1.49 (1.35, 1.65)	1.51 (1.36, 1.68)
Patient age					
18 - 47.5 years	663	42.2	15.7	Ref.	Ref.
47.6 - 59.5 years	925	76.2	12.1	0.84 (0.74, 0.96)	0.66 (0.58, 0.74)
59.6 - 70.5 years	943	86.4	10.9	0.81 (0.72, 0.92)	0.57 (0.50, 0.65)
> 70.5 years	968	59.0	16.4	1.19 (1.04, 1.35)	0.77 (0.67, 0.89)
Sex					
Males	1253	107.0	11.7	Ref.	Ref.
Females	2246	156.7	14.3	1.19 (1.09, 1.30)	1.12 (1.02, 1.24)
Charlson Index					
0	2388	185.3	12.9	Ref.	Ref.
≥ 1	1111	78.4	14.2	1.12 (1.02, 1.22)	0.91 (0.83, 1.00)
Number of drugs					
1 - 2 drugs	128	29.4	4.4	Ref.	Ref.
3 - 4 drugs	378	50.3	7.5	1.86 (1.52, 2.28)	1.99 (1.63, 2.45)
5 - 7 drugs	902	74.4	12.1	3.10 (2.56, 3.75)	3.46 (2.85, 4.21)
≥ 8 drugs	2091	109.6	19.1	4.94 (4.1, 5.94)	5.77 (4.77, 6.97)
Continuity of care index		Mean, SD			
(HR: per 1 unit)		1.09(0.63)		1.22 (1.16, 1.30)	1.20 (1.13, 1.27)

* - antihistamines, blood and coagulation, anti-neoplastics

Table 7.3 Frequency distribution of adverse drug events documented by electronic health record classified according to MedDra.

MeDdra System Organ Class (SOC)	N	%
Gastrointestinal disorders	**244**	**22.1**
Nausea	57	5.2
Diarrhea	38	3.4
Abdominal pain	33	3.0
Dyspepsia	22	2.0
Dry mouth	15	1.4
Nervous system disorders	**154**	**14.0**
Headache	56	5.1
Dizziness	22	2.0
somnolence	20	1.8
Drowsiness	11	1.0
Tremor	10	0.9
Respiratory, thoracic and mediastinal disorders	**114**	**10.3**
Dry cough	43	3.9
Cough	39	3.5
Epistaxis	13	1.2
Dyspnea	5	0.5
Nasal dryness	5	0.5
Throat irritation	2	0.2
Musculoskeletal and connective tissue disorders	**108**	**9.8**
Myalgia	59	5.3
Joint pain	10	0.9
Leg cramps	6	0.5
Muscle cramps	6	0.5
Muscle weakness	5	0.5
Metabolism and nutrition disorders	**87**	**7.9**
Hypoglycemia	34	3.1
Hyponatremia	12	1.1
Hypokalemia	10	0.9
Hyperkalemia	7	0.6
Hyperuricemia	7	0.6
Psychiatric disorders	**74**	**6.7**
Insomnia	22	2.0
Anxiety	15	1.4
Agitation	14	1.3
Confusion	4	0.4
Depression	4	0.4
General disorders and administration site conditions	**74**	**6.7**
Edema	17	1.5
Fatigue	12	1.1

Table 7.3 (continued). Frequency distribution of adverse drug events documented by electronic health record classified according to MedDra.

MeDdra System Organ Class (SOC)	N	%
Lightheadedness	9	0.8
Peripheral edema	8	0.7
Edema limbs	5	0.5
Skin and subcutaneous tissue disorders	**51**	**4.6**
Pruritus	8	0.7
Sweating increased	5	0.5
Skin rash	4	0.4
Allergic rash	3	0.3
Dermatitis	3	0.3
Vascular disorders	**51**	**4.6**
Hypotension	26	2.4
Orthostatic hypotension	12	1.1
Flushing	4	0.4
Hot flashes	4	0.4
Hypertension	2	0.2
Cardiac disorders	**38**	**3.4**
Palpitations	17	1.5
Bradycardia	6	0.5
Tachycardia	5	0.5
Sinus bradycardia	2	0.2
Angina pectoris	1	0.1
Reproductive system and breast disorders	**35**	**3.2**
Erectile dysfunction	7	0.6
Sexual dysfunction	5	0.5
Spotting	5	0.5
Libido decreased	4	0.4
Menorrhagia	4	0.4
Investigations	**12**	**1.1**
Weight gain	9	0.8
Creatinine increased	2	0.2
Creatine phosphokinase increased	1	0.1
Renal and urinary disorders	**14**	**1.3**
Renal insufficiency	5	0.5
Polyuria	3	0.3
Urinary frequency	3	0.3
Nocturia	1	0.1
Urinary incontinence	1	0.1

Table 7.3 (continued). Frequency distribution of adverse drug events documented by electronic health record classified according to MedDra.

MeDdra System Organ Class (SOC)	N	%
Ear and labyrinth disorders	**10**	**0.9**
Vertigo	8	0.7
Infections and infestations	**9**	**0.8**
Oral candidiasis	2	0.2
Injury, poisoning and procedural complications	**6**	**0.5**
Fall	6	0.5
Immune system disorders	**2**	**0.2**
Cytokine release syndrome	2	0.2
Hepatobiliary disorders	**3**	**0.3**
Hepatitis	2	0.2
Blood and lymphatic system disorders	**9**	**0.8**
Bleeding	4	0.4
Eye disorders	**3**	**0.3**
Xerosis	1	0.1

Figure 7.1 Cumulative hazard ratio for on-label and off-label use

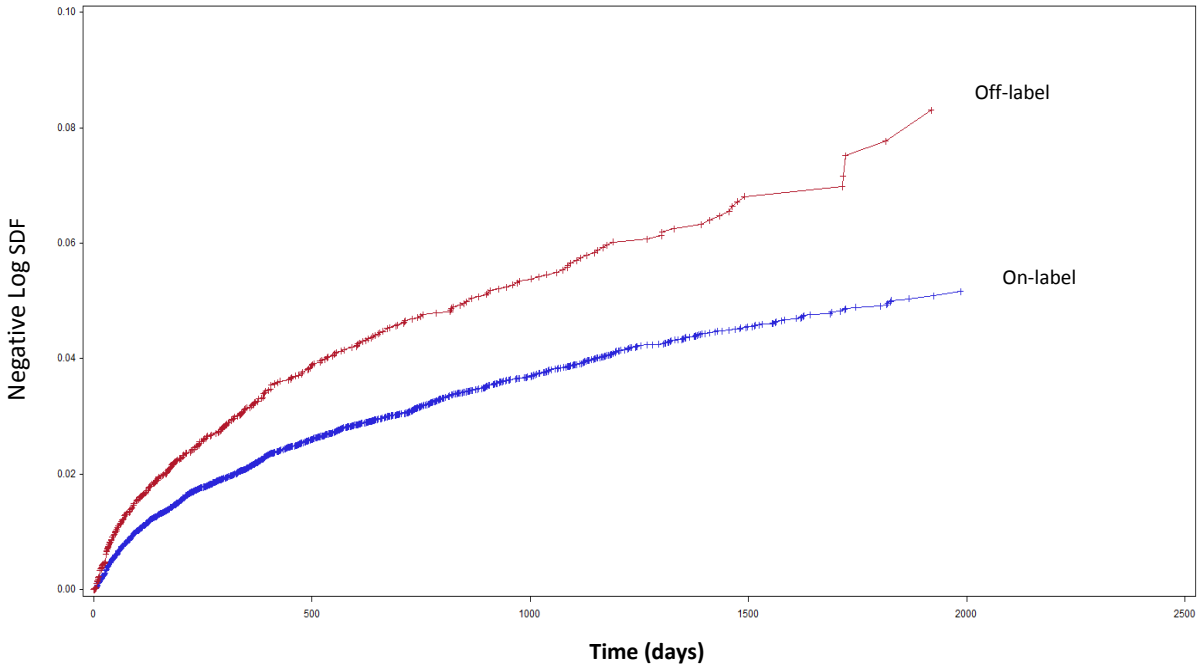
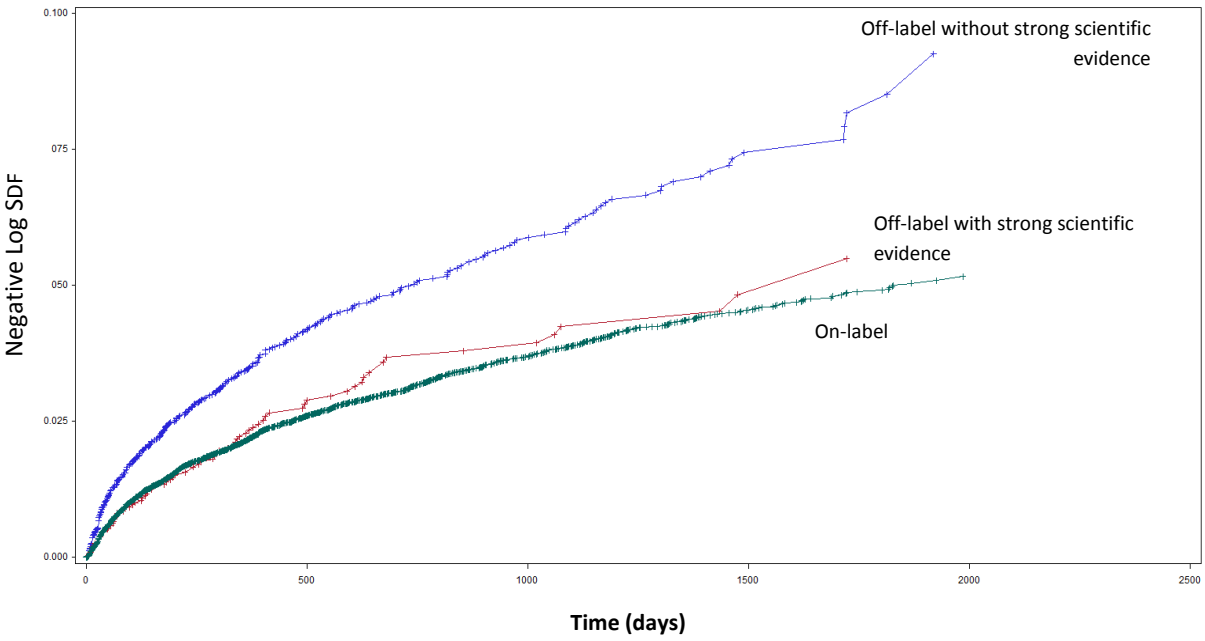


Figure 7.2 Cumulative hazard ratio for on-label use, off-label use with strong scientific evidence and off-label use without strong scientific evidence.



Chapter 8: Discussion

Summary of findings

The first manuscript determined if drug discontinuation and dose-change orders documented in an EHR system could accurately detect physician-identified adverse drug events and other treatment outcomes. It was found that physician's drug discontinuation and dose-change orders and their associated reasons, were recorded with good accuracy. There was high concordance between the reasons in the EHR system and the medical chart. Recommendations that emerged from this study were to develop separate lists of reasons for discontinuing a drug and changing the dose of a drug to enhance accuracy and ease of data entry.

The second manuscript assessed the accuracy of treatment indication recorded at the point of care in an electronic prescribing application and how well this documentation measured off-label prescribing. It was demonstrated that physician-facilitated chart review was a feasible approach to review medical charts, especially if the aim is to link drugs with their treatment indication. It was also shown that treatment indication was recorded with high sensitivity (completeness) and positive predictive value (correctness) using an electronic prescribing system. Moreover, the treatment indication data could be used to detect off-label drug prescriptions.

The third manuscript used drug prescription and treatment indication data from an EHR platform (validated in our second manuscript) to measure the prevalence of off-label prescribing in an adult population and investigate the drug, patient and physician determinants of off-label prescribing. The comprehensive nature of our data allowed identification of treatment indications associated with a high prevalence of off-label drug use that would benefit from new drug development or RCTs. It reported that 11% of drugs were prescribed off-label and that, among these, 79% lacked strong scientific evidence. Off-label prescribing was highest for central nervous system drugs, including anticonvulsants, antipsychotics, and antidepressants and off-label prescribing was lowest for formulary-restricted drugs. Drugs with only one or two approved indications were associated with high

off-label use compared with drugs with three or more approved indications. Drugs approved after 1995 were prescribed off-label less often than were drugs approved before 1981. Patients with Charlson Comorbidity Index of one or higher had lower off-label use than did patients with an index of zero. Physicians with an evidence-base orientation (as measured by Evidence-Practicality-Conformity Scale) were less likely to prescribe off-label. Moreover, physicians who graduated before 1980 prescribed off-label without scientific evidence less frequently than physicians who graduated after the 1980s'. The top indications treated with off-label drugs included nocturnal leg pain, benign positional vertigo, neurogenic pain, fibromyalgia, arrhythmia, generalized anxiety disorder, and insomnia.

The fourth manuscript investigated the association between off-label use and adverse drug events, by using data validated in manuscript one and two as well as knowledge about the prevalence and determinants of off-label prescribing (manuscript three). It was found that off-label use independently predicted ADEs. Anti-infective drugs had the highest incident rate of ADE. Patients who received more than eight drugs had six-fold increased risk of ADEs compared to patients with one to two drugs; a dose-response relationship was observed between the number of drug prescriptions and the risk for an ADE. Young adults and women had higher risk of ADE compared to the three older quartiles and men, respectively. Patients who were prescribed drugs approved after 1981 had a greater risk of ADE than those who were prescribed drugs approved before 1981. Higher rates of ADE were observed in patients with higher continuity of care. This study demonstrated that physician-identified adverse drug events could be documented and off-label use of drugs could be monitored in an outpatient setting using an EHR.

Strengths and limitations

The research described in the first and second manuscript has several strengths and limitations. The strengths include the administration of physician-facilitated chart review soon after patients' visits which helped to decrease recall bias from the physicians. In addition, blinding the interviewers and physicians to the treatment change status in the EHR system controlled potential sources of measurement bias. Verification bias (overestimation of sensitivity and underestimation of specificity) was avoided by adjusting for the stratified

sampling scheme used in the selection of treatment discontinuation. In our second manuscript, the physician-facilitated chart reviews allowed us to accurately link drug prescriptions to their treatment indications. Since drugs and medical problems (or diagnoses) are written on the medical chart separately, linking prescriptions and treatment indications would have been difficult, especially if the drug was prescribed for an off-label indication. The distribution of treatment indications in the study was comparable to the distribution of treated health problems in Canada where the top eight indications in this study are among the ten top diagnoses treated with drugs (375).

One limitation of the studies is that physicians were aware of the close monitoring of their behavior during the study period. This could have resulted in a possible increase in the sensitivity of the system if they recorded more treatment changes during the study. However, the treatment change rate changed by less than 0.11% during the study period. Second, while our findings cannot be extrapolated to all physicians, they may be generalized to clinical settings where recording of drug treatment changes and treatment indications in EHR is mandatory and where physicians are well versed in using a computerized prescribing system.

Third, electronic orders for treatment change do not capture severe reactions and deaths. If electronic prescribing systems were combined with administrative data to determine mortality and hospital admissions, a more sensitive and comprehensive pharmacosurveillance system may be possible. Fourth, one reason the EHR system failed to correctly capture some treatment indications was the inability to identify and provide all off-label indications within the electronic system to physicians. While free-text entry is part of the application, the lack of standardization hampers the usability of the data. The creation of a searchable indication list from the treatment indication database should address this problem.

The third study has several strengths. The first strength was the use of prescribing data in an EHR platform that explicitly linked treatment indications to prescribed drugs to evaluate, for the first time, the prevalence of off-label prescribing in primary care settings. Second, the drug-treatment indication data recorded at the time of drug prescribing was validated by chart review using the medical chart and input from the treating physician. Third, the scientific evidence for off-label uses was categorized by using a recognized compendia and a

previously published method (33). Fourth, drug, patient and physician determinants were investigated with the appropriate statistical methodology to account for the three levels of clustering. This study also has some limitations. First, off-label prescribing was defined conservatively; and did not include dosage, frequency, route of administration, duration of treatment, or age range, which, if considered, would increase the prevalence of off-label prescribing. Second, some off-label use may be explained by co-morbidities; however, the potential for misclassification was low considering our explicit linking of drugs with their indications. Third, the compendium used to evaluate the scientific evidence for off-label use is not transparent and not completely up-to-date; however, this compendium documents a comprehensive list of off-label indications with their level of scientific evidence better than other compendia (33;341). Fourth, the physicians in the study were younger and more willing to use an EHR than other physician groups; this may limit the generalizability of the findings. Fifth, because we did not capture non-pharmacologic treatments and their indications, the findings are conditional on having a drug prescribed for an indication. The prevalence of off-label prescribing could not be directly compared with previous studies since documentation of treatment indications and inclusion/exclusion of study subjects and drugs were completely different.

The fourth study has several strengths. First, on-label/off-label status of drug treatment comes from an EHR which linked drugs to their treatment indication at the time of prescribing, and the linkage was verified to have high completeness and correctness. Second, ADEs were captured during a patient-physician encounter with mandatory reporting of reasons for discontinuation of treatment. Third, the use of a marginal Cox model for clustered survival analysis with a robust sandwich covariance estimator to account for the intra-cluster dependence of drugs within patients, curtailed spurious association between exposures and outcome. Fourth, it was demonstrated that physicians can document treatment outcomes (specifically ADEs) at the point-of-care. The study has several limitations. First, ADE identification depends on physicians and patients, but physicians may not identify medication-related symptoms and patients may not report all symptoms (43). Second, ADEs in patients with comorbidities may not be readily ascribed to the specific drugs. Third, patients with severe ADEs may visit hospitals and other physicians, and the ADE may not be recorded in the EHR. These limitations may have resulted in

underestimation of the ADE incidence, but the underestimation will affect both on- and off-label uses, limiting differential bias.

Implications of thesis findings

In this thesis, it was shown that an EHR system can accurately document physician-identified adverse drug events and treatment indications, and that this documentation can be easily integrated into the clinical work flow. The treatment indication data could be used to measure prevalence of off-label use and identify important determinants of off-label use which included drug, patient and physician characteristics. In addition, the treatment indication data could be combined with drug treatment outcome data to create a novel pharmacosurveillance tool. Moreover, it was demonstrated that off-label prescribing is an independent determinant of adverse drug events.

Implications for EHRs and drug safety research

The implementation of information technology and EHRs has created new information sources that can be used to conduct drug safety and effectiveness evaluations (e.g. GPRD). Early introduction of computerized dispensing has paved the way for successful implementation of prescription event monitoring in the United Kingdom and New Zealand (52;362). Recently, governments have begun to spend billions of dollars to implement EHRs (376;377). This investment presents a timely opportunity to identify critical elements of health data that can be used to evaluate the safety and effectiveness of drugs, including treatment indications, treatment outcomes (e.g. discontinuation of a drug due to ADEs or ineffectiveness) and specific adverse drug events. Furthermore, as standards and financing of computerization of health care is primarily determined by national and regional health authorities, certification processes for required features are already in place. For example, in the United States, objectives for "meaningful use" of EHRs were defined to achieve improvement in health care quality (387). Maintaining an active medication and problem (diagnosis) list were among the core objectives identified to create an electronic medical record. These two tasks are seamlessly integrated in the MOXXI EHR, which generates medication and problem lists in real-time. Linking a prescribed drug with an indication could be a meaningful use objective. Our study suggests there may be a substantial benefit to

adding of the rationale for treatment change orders as a required feature for certification. EHR vendors and users have demonstrated the willingness and creativity to include new features in electronic prescribing systems (361;362). The equivalent to "the meaningful use" in Canada was termed "clinical value" with some parallel with the United States system (402). Broad-scale, international adoption of EHRs is critical, both to detect rare events and to minimize potential biases from selective participation.

Implications for monitoring of off-label use and pharmacosurveillance

It was demonstrated that the life-cycle of drugs can be tracked by documenting the reasons for initiating the treatment and the reasons for its discontinuation in an EHR. This method enhances the current methods of pharmacosurveillance, including spontaneous reporting of adverse drug events, prescription event monitoring (PEM), case-control and cohort studies using administrative and computerized databases. A recent review (26) by Dr. Dal Pan (April 5, 2012), the director of Office of Surveillance and Epidemiology of the FDA, underlines the need to study adverse events that occur in off-label situations and outlines several post-marketing surveillance methods. The review has described the most important limitation of the current methods as:

> "A hurdle to the study of the safety of off-label use of drugs is the lack of accurate information on why a particular medicine is prescribed to a particular patient. Lack of information on indication for use limits the utility of both spontaneous case reports and many types of observational data, including drug utilization data, in safety studies of off-label use."

The review also identified the study reported in manuscript two in this thesis as one of the 'Emerging Sources of Information on the Safety of Off-Label Use of Medicines'.

As it was demonstrated, drugs can be identified according to their treatment indication as on- or off-label and the strength of scientific evidence for their off-label use. Additionally, these drug-indication data are also linked to treatment outcomes such as ADEs or ineffective treatment. These can be used for pharmacoepidemiologic safety and effectiveness studies. Moreover, the drug, treatment indication and ADE data along with the patient demographic, and concomitant problems and drugs could be sent to drug regulatory bodies for further evaluation as shown by Aster project in Boston (46).

Documentation of adverse drug events in EHRs and linking to drug-indication data and other clinical parameters (functional status, laboratory results) at a larger scale of (province or country) will create a knowledge-generating capacity (45) that will ultimately change how medicine is practiced, and how computerized decision support systems are developed. Having the treatment indication data of a new drug immediately after it is release on thousands of prescriptions would considerably enhance our understanding of how medicine is practiced and if linked to outcome data it will have a transforming potential for both practice and pharmacosurveillance.

Implications for drug regulatory bodies

In recent years, drug regulatory bodies have created mechanisms such as the priority review, notice of compliance with condition (NOC/c), the expedited review, and accelerated approval to expedite the drug review process and allow rapid access of drugs to the public. For example, the European Union (European Medicines Agency Road Map Initiative), USA (Food and Drug Administration Amendments Act of 2007) and Canada (Progressive licensing framework for drug approval) have mandated or are in the process of mandating the life-cycle approach to drug evaluation with its greater emphasis on ongoing pharmacovigilance than traditional pre-marketing approval (109;111). The principle of the life-cycle approach includes specific commitments for post-marketing studies and risk management plans at the time of drug submission, including drug utilization studies that describe how a drug is marketed, prescribed, and used (403). Specifically, the European Union has outlined its plans to collect information on the 'real life' use of medicine, including off-label uses for a continuous risk-benefit evaluation to encourage safe and rational use of drugs (404). Among others, the US risk evaluation and mitigation strategies include confining prescribing to on-label indications where the benefit outweighs the side effects for certain drugs with known risk (405). In addition, FDA's commitment to ensure safety throughout the life-cycle of the drug also focuses on adverse events which occur in off-label use (406). I believe Health Canada needs to monitor off-label use as it moves towards a progressive licensing framework of drug approval. A new paradigm of drug approval is becoming a reality, where new drugs get earlier market access with the potential of more drug safety problems. As a result, we need to strengthen pharmacosurveillance and

develop new methods to balance the new system of drug approval and post-marketing evaluation.

Implications for prescribing physicians

The studies reported in this thesis demonstrated how active participation of physicians can facilitate the implementation of new features in electronic health records in an ambulatory care setting and advance patient safety research. Some clinicians believe that documentation of treatment indications and outcomes is not possible; these studies proved that not only is it possible, but that the data could be used to answer important pharmacoepidemiologic questions. Documentation of treatment indication is one value-added feature for the physicians, which facilitated the creation of a problem list of active and current diagnoses as well as allowing automated check for drug-disease interactions. These studies demonstrated that EHR implementation would be greatly aided if clinically relevant features are added to electronic systems.

Physicians have broad discretion on drug prescribing as long as they focus on the best interest of the patient (158). For example, manuscript three identified treatment indications where there is no Health Canada approved drug, so that physicians treated these conditions with available drugs. However, four in five off-label prescriptions have little or no scientific evidence and that these prescriptions led to more adverse drug events. This diverse spectrum of off-label use shows that physicians and physician organizations need to recognize the diversity as well as the lack of scientific evidence for most off-label drug use. We cannot explain every off-label prescription as 'clinically plausible' or their being a 'lack of an alternative drug' or simply to 'patient complexity'. Lack of knowledge of approved treatment indication (164) was demonstrated to be one factor for off-label prescribing. The vast amount of drug information (393) also contributes to off-label prescribing. We need to acknowledge that the lack of knowledge about drugs and the difficulty of keeping up with the ever-changing drug information are affecting how well patients are treated. Using computerized decision support systems, we could fill the knowledge gap by supplying drug approval status and the degree of scientific evidence at the point-of-care. For example, in a system like MOXXI, we could feasibly color-code off-label treatment indications, and the degree of scientific evidence. Additionally, we could record the treatment indication before

the drug prescription, (indication-based prescribing or ordering by indication), allowing the software to offer a drug recommendation for particular indications (393). The selection could depend on the drug approval status for the indication, the strength of scientific evidence, or recommendations from systematic reviews or compendia, or clinical guidelines from professional organizations.

Physicians' with an evidence-based orientation were less likely to prescribe off-label, particularly in cases where the off-label prescription lacked strong scientific evidence. This observation implies that physicians who emphasize evidence-based medicine base their treatment decisions not only on data from drug regulatory bodies but also using the evidence available in peer-reviewed publications, clinical guidelines and recommendations from professional societies. Currently, there is an effort to educate physicians on the supporting evidence for off-label uses (251;385;386) with the aim of linking off-label use to rigorous outcome evaluation, with the physician being an active participant in evidence development. Connecting drugs with their treatment indications and providing evidence to support off-label use at the time of prescribing may address scientifically unsupported off-label use.

One goal of physician training is to produce informed physicians who act in the best interest of their patients. The 'best interest of the patient' includes whether the drug treatment is necessary in the first place, whether it is approved by Health Canada, whether there is strong evidence to prescribe the drug for the condition, how safe is the drug in treating the health condition, the availability of alternative drugs, and how costly the drug is, among others. The history of pharmaceuticals and their regulation go hand-in-hand with physician autonomy. A century ago, physicians prescribed anything they thought to be a drug. In the 1930s concepts of drug safety were introduced, and during the 1960s concepts of drug efficacy and monitoring of adverse drug reactions were added to drug regulation (407). The recent introduction of concept of risk management of drugs may allow patients to have earlier access to drugs, while curtailing the discretion given to physicians to prescribe any drug for any indication (405). Professional medical organizations and medical schools need to become active participants in drug regulation by creating informed physicians or lose progressively their autonomy in drug prescription.

Implications for patients

It was shown that patients who had inadequate information and concerns with their medications were less adherent to prescribed drug (408). Patients who receive myriads of drugs, be it for on- or off-label conditions, need to be informed of the treatment indication, which drug was prescribed for that indication, and whether the drug is approved for that specific condition or there is strong evidence for its use and the availability of other modalities of drug or other treatments. The patient needs to be an active participant in drug selection since benefit-risk ratios are best evaluated by the person taking the risk. Life-threatening conditions and conditions with no alternatives or when other drug treatments fail may justify the risk involved in taking a drug for an off-label indication. At the same time, patients are untapped resources for the evaluation of off-label uses of drugs as demonstrated in projects like PatientsLikeMe (129) : as patients could be supported to be more actively involved in reporting of adverse drug events, participating in studies of off-label uses, as well as real-world comparative effectiveness studies and be active participants in the discussion of off-label drug policies. Moreover, inclusion of treatment indication in the prescription would also help pharmacists direct patient education to the specific disease entity, would increase detection of prescribing problems and decrease dispensing errors (409).

Implications for the Pharmaceutical industry

I believe the pharmaceutical industry needs to be an active participant in monitoring off-label use and its effect and the development of new methods of pharmacosurveillance. Monitoring off-label use is becoming one feature of the risk management strategy for drug regulatory bodies. Adopting new and proactive approaches to pharmacosurveillance and off-label use earlier will benefit the industry in terms of avoiding delays in introduction of new drugs, the preparation for periodic drug evaluations and reports.

Current methods of pharmacosurveillance have numerous limitations and have resulted in several knee-jerk reactions from the media, the public and the drug regulatory bodies about drugs and the pharmaceutical industry whenever unfavorable safety data are reported (45). Proactive pharmacoepidemiological methods which address important drug safety question is needed which can harness the development occurring in EHR. The pharmaceutical

industry need to take the lead in these endeavors by sponsoring students, researchers and research programs; with an arm length arrangement to stifle conflict of interest issues.

As several US court rulings and billions of dollars in settlement claims have shown, the pharmaceutical companies' need to refrain from illegal promotion of off-label use. The short-term gain is offset by the long-term harm to the innovativeness of the industry and the public trust.

Implications for funding of research involving off-patent drugs

Older drugs have higher prevalence of off-label use. We need to synthesize evidence on the off-label use of these drugs where studies exist, and perform studies when evidence is lacking. Since the incentive for the pharmaceutical industry is limited for off-patent drugs, public research organization (e.g. CIHR, NIH) need to create a mechanism of funding these studies.

Implications for funding for innovative EHR

The strong interest in this research, by both the medical community (manuscript 3 was published online first and accompanied by an editorial) and the mainstream media (Appendix C), indicates that EHRs (such as MOXXI) fill an important gap in clinical and applied research and may be used as foundations for future EHRs. Governments and funders need to create special financing mechanisms to allow continuous development of innovative and cutting-edge value-added features in EHR systems.

Implication for pharmacoepidemiologic studies and confounding by 'indication'

Currently, propensity score technique is a popular method of reducing bias due to confounding by indication in observational studies. Among the variety of reasons for drug treatment, the first requirement is having a medical condition (treatment indication) and other, less obvious characteristics of the patient and the physician determine the selection of a particular drug for the treatment (266). The linkage of drugs with their treatment indication will allow identification of patients with a particular indication (or subgroup population) and facilitate correct specification of propensity score created from the less

explicit characteristics of the patient and the physician that determine the choice of the drug (410).

Future studies

Develop a pharmacosurveillance system that provides accurate information on the safety and effectiveness of prescription drugs

Future research should investigate how EHR data improves ADE detection in new users of commonly used drug groups (e.g. anti-hypertensive drugs, non-steroidal anti-inflammatory drugs, and anti-depressants) when compared to using administrative data alone. Furthermore, research should estimate the extent to which the accuracy of adverse drug event detection is influenced by treatment indication status (on- vs. off-label), the severity of the adverse event, and patient age, sex and co-morbidity.

Large scale implementation of treatment indication and treatment outcome features in primary care and hospital settings

The documentation of reasons for discontinuation of medications (manuscript one) was mirrored by a Dutch study in a hospital setting (411). It was implemented in an EHR for better communication between health professionals and different care settings and for pharmacovigilance activity. Future research should focus on implementation of documentation of treatment outcomes and treatment indications in EHRs in multiple jurisdictions and should evaluate the effect on pharmacosurveillance activities.

Evaluation of reporting safety and effectiveness data in an EHR system

In a controlled trial, future research should investigate the effect of a large-scale implementation of a pharmacosurveillance system in an EHR platform to improve drug safety and effectiveness by providing real-time feedback about drug safety and effectiveness data at the point-of-care.

Off-label prescribing as alerts and warnings in EHR and feed-back to physicians on off-label prescribing.

Using computerized decision support systems, we could fill the drug-knowledge gap by supplying drug approval status and the degree of scientific evidence at the point-of-care. One can feasibly color-code off-label treatment indications, and the degree of scientific evidence attached to these uses. Physicians could be alerted with computerized alerts when a dangerous off-label uses is identified. Moreover, prevalence of off-label prescribing with and without scientific evidence can be calculated at level of a physician and this information can be used to create an annual or a bi-annual report pertaining to a particular physician in comparison to her colleagues. Future research should investigate the value of presenting this information to EHR systems and to physicians.

Towards indication-based prescribing

While MOXXI was designed to require a treatment indication to be selected after the drug is entered into the system, the reverse is also possible. Evidence-based criteria could be used to suggest drugs according to the profile of the patient and the indication for treatment. The impact of indication-based prescribing could be evaluated by measuring medication errors, guideline aligned prescribing, ease of professional communication (e.g. physicians and pharmacists), and work flow efficiency.

Towards integration of ADE data generated in EHR systems to regulatory bodies (Health Canada)

Canada is moving towards progressive licensing of drugs, we need to develop new pharmacosurveillance methods during the post-marketing phase. As a result, we need to create a mechanism of forwarding data generated using the MOXXI EHR to Health Canada for further evaluation and incorporation into the adverse drug event reporting system, as shown in the US (46).

Conclusions

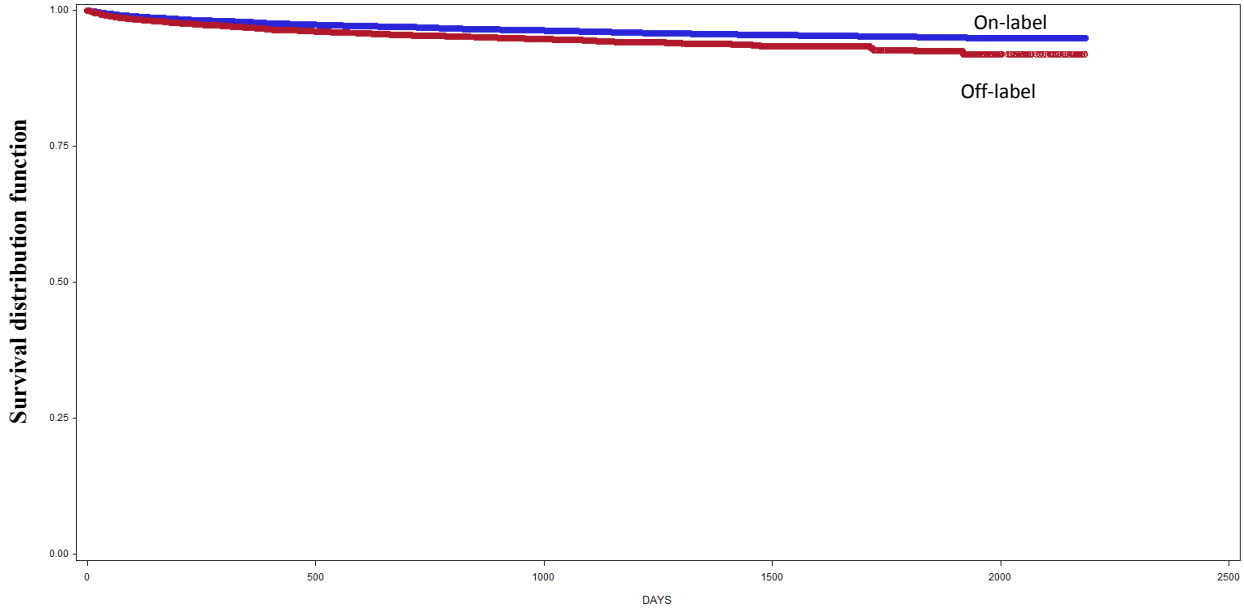
In this thesis, I have shown for the first time that an EHR system can accurately document physician-identified treatment indications and adverse drug events and other treatment outcomes, and that this documentation can be easily integrated into the clinical work flow. The treatment indication data could be used to measure prevalence of off-label use and identify important determinants of off-label use which included drug, patient and physician characteristics. In addition, the treatment indication data could be combined with drug treatment outcome data to create a novel pharmacosurveillance tool. Moreover, it was demonstrated that off-label prescribing is an independent determinant of adverse drug events. Future EHRs should be designed to enable post-market surveillance of drugs by incorporating treatment indications and treatment outcomes to monitor the safety and effectiveness of on- and off-label uses of drugs.

Appendices

Appendix A. Additional material for Manuscript 4

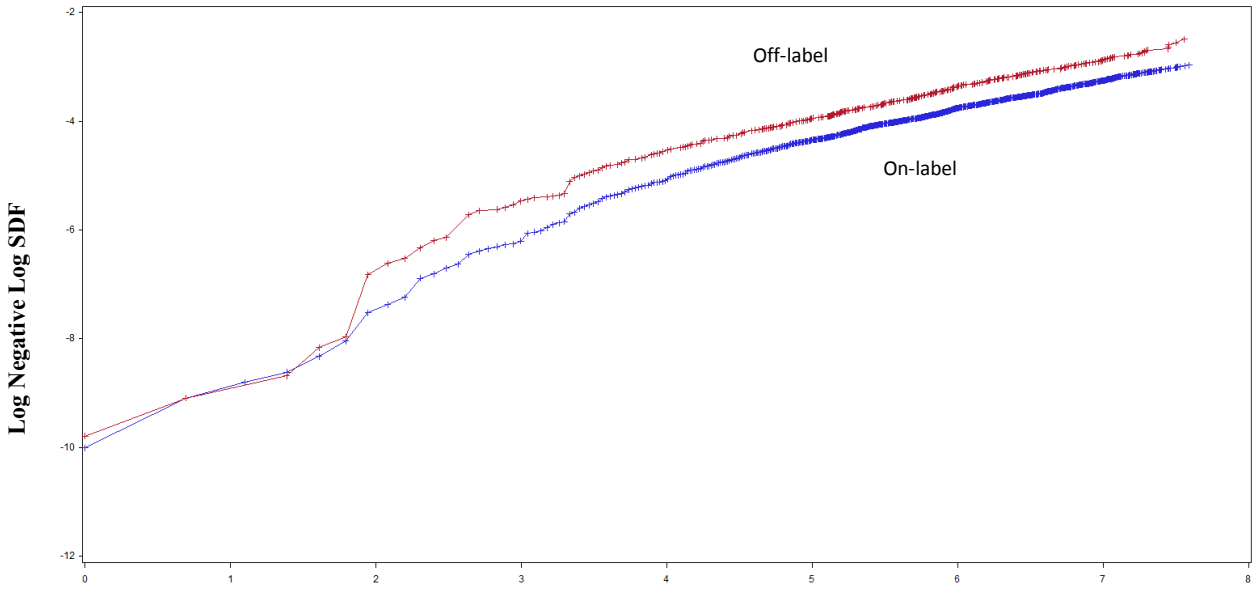
Survival curves, Martingale residual graphs, Schoenfeld residual graphs and GEE Poisson regression results

Appendix A.1 Survival curves comparing on-label and off-label use



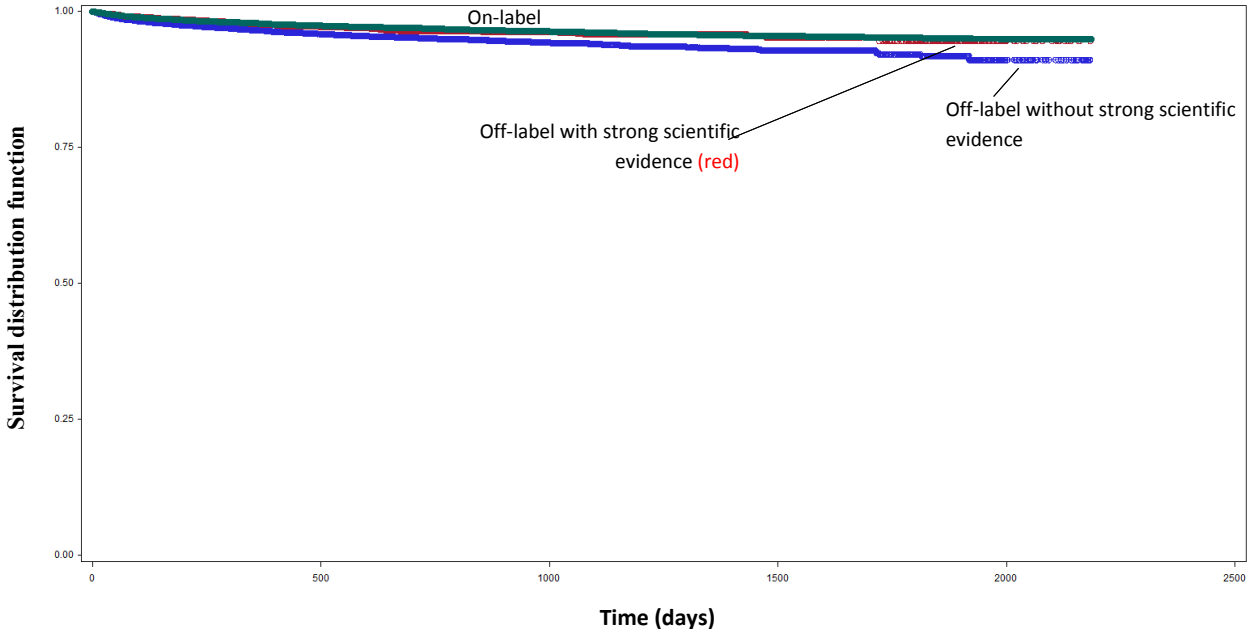
Time (days)

Appendix A.2 Log negative log survival curves comparing on-label and off-label use

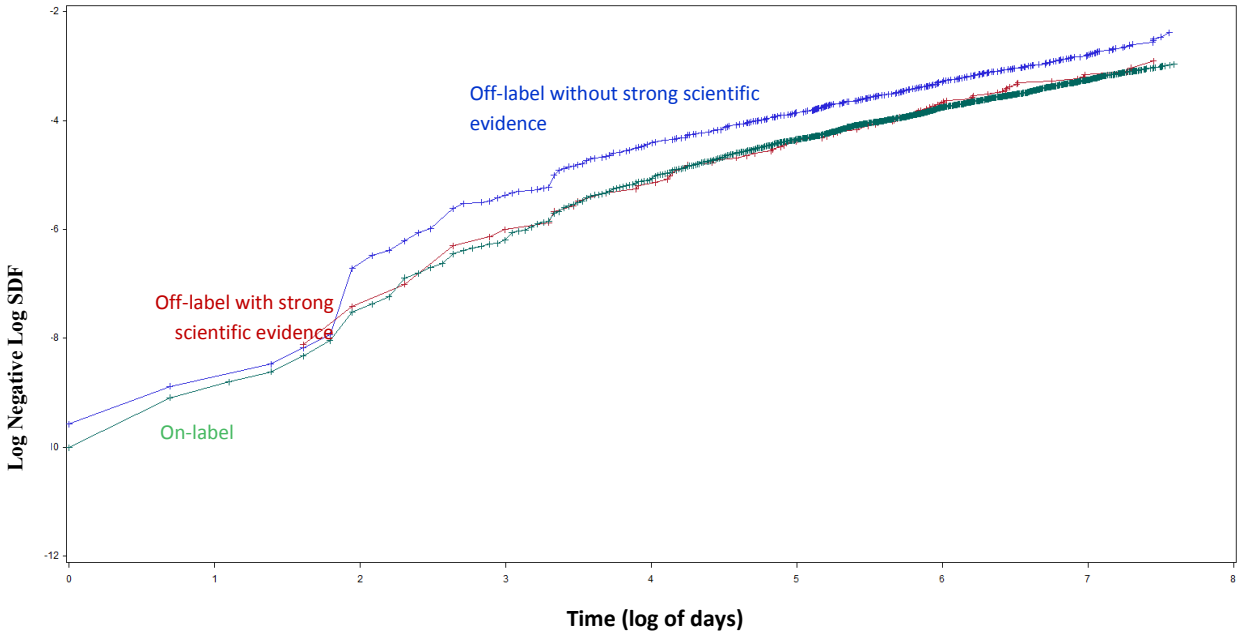


Time (log of days)

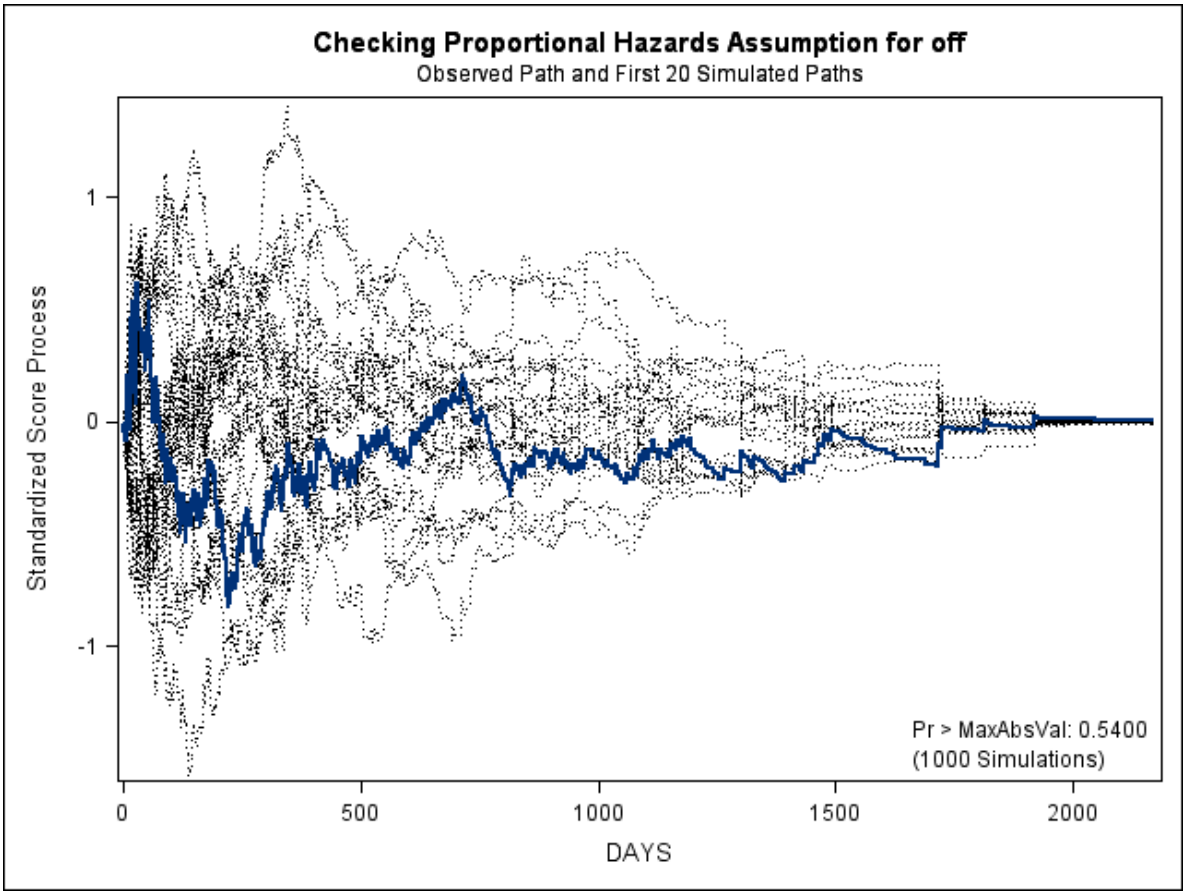
Appendix A.3 Survival curves comparing on-label, off-label use with and without strong scientific evidence



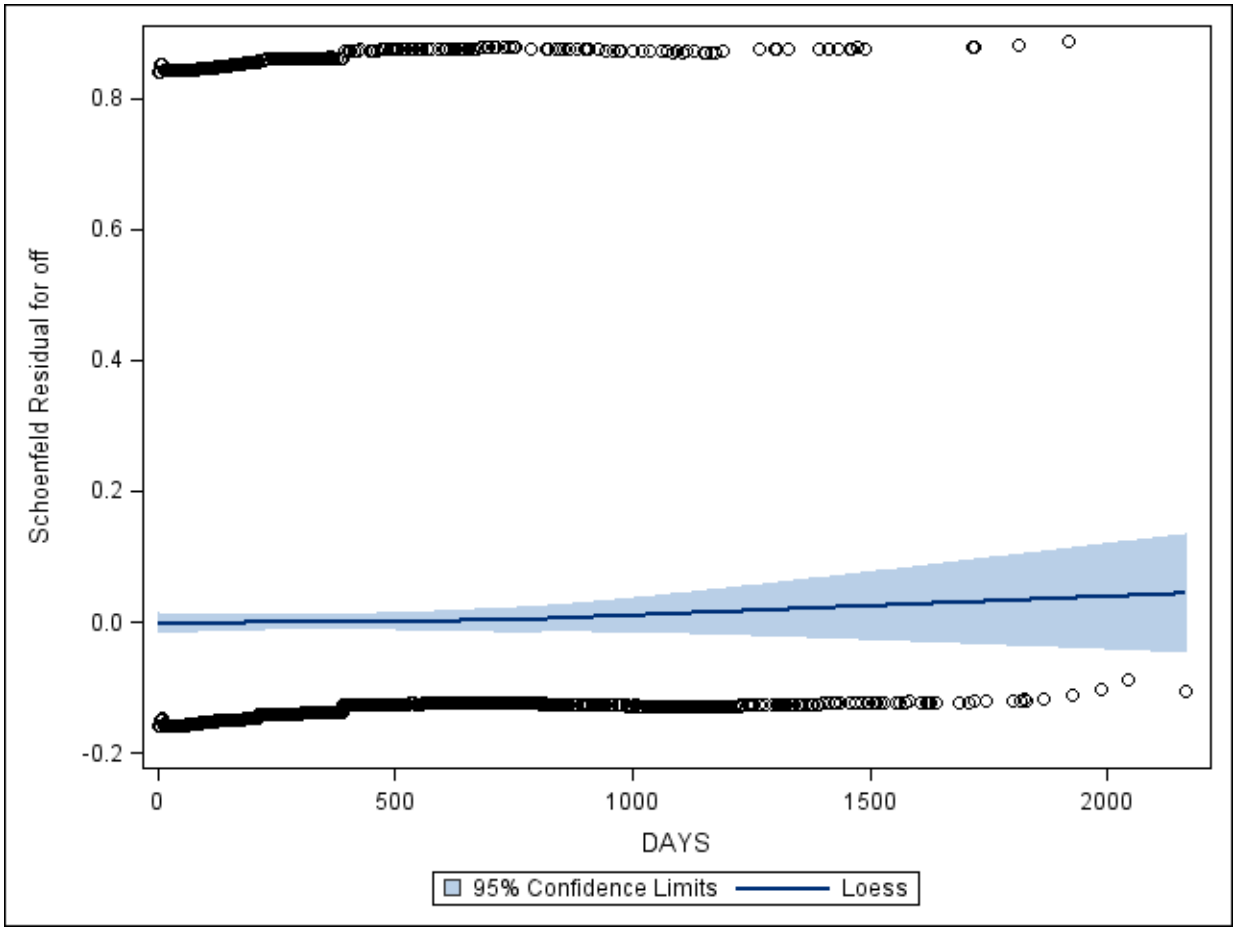
Appendix A.4 Log negative log survival curves comparing on-label, off-label use with and without strong scientific evidence



Appendix A.5 Proportionality hazard assumption for off-label variable using martingale residuals.



Appendix A.5 Proportionality hazard assumption for off-label variable using Schoenfeld residuals.



Appendix A.6 Comparison between marginal Cox regression and GEE Poisson regression

	Cox regression	Poisson regression
Off-label and scientific evidence		
On-label	Ref.	Ref.
Off-label with strong evidence	1.11 (0.88, 1.39)	1.09 (0.87, 1.37)
Off-label without strong evidence	1.53 (1.37, 1.72)	1.55 (1.38, 1.74)
AHFS Class		
Gastrointestinal	Ref.	Ref.
CNS	2.97 (2.39, 3.68)	3.11 (2.98, 3.25)
ENT	0.43 (0.28, 0.66)	0.44 (0.25, 0.49)
Hormone and synthetics	2.55 (2.03, 3.20)	2.57 (2.47, 2.66)
Formulary-restricted	1.90 (1.44, 2.51)	1.85 (1.83, 1.86)
Anti-infectives	6.08 (4.39, 8.43)	11.4 (11.2, 11.6)
Autonomic	1.64 (1.11, 2.43)	1.62 (1.51, 1.73)
Cardiovascular	3.40 (2.75, 4.21)	3.33 (3.18, 3.48)
Others*	0.22 (0.14, 0.36)	0.26 (0.16, 0.26)
Drug age		
Before 1981	Ref.	Ref.
1981- 1995	1.59 (1.42, 1.77)	1.58 (1.42, 1.77)
1996 - 2009	1.51 (1.36, 1.68)	1.52 (1.36, 1.70)
Patient age		
18 - 47.5 years	Ref.	Ref.
47.6 - 59.5 years	0.66 (0.58, 0.74)	0.62 (0.54, 0.70)
59.6 - 70.5 years	0.57 (0.50, 0.65)	0.51 (0.45, 0.58)
> 70.5 years	0.77 (0.67, 0.89)	0.72 (0.62, 0.83)
Sex		
Males	Ref.	Ref.
Females	1.12 (1.02, 1.24)	1.13 (1.02, 1.24)
Charlson Index		
0	Ref.	Ref.
≥ 1	0.91 (0.83, 1.00)	0.92 (0.841.01)
Number of drugs		
1 - 2 drugs	Ref.	Ref.
3 - 4 drugs	1.99 (1.63, 2.45)	1.89 (1.54, 2.32)
5 - 7 drugs	3.46 (2.85, 4.21)	3.19 (2.62, 3.89)
≥ 8 drugs	5.77 (4.77, 6.97)	5.21 (4.31, 6.30)
Continuity of care		
(HR: per 1 unit)	1.20 (1.13, 1.27)	1.26 (1.18, 1.34)

Appendix B: Copy of published articles included in the thesis

ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (11): 1005-1016
0114-5916/08/0011-1005/$48.00/0

Detection of Adverse Drug Events and Other Treatment Outcomes Using an Electronic Prescribing System

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Abstract

Background: Current pharmacosurveillance methods do not provide timely information on drug safety and effectiveness. Real-time surveillance using electronic prescribing systems could address this problem; however, the data collected using these systems has not been validated. We investigated the accuracy of using orders for drug discontinuation and dose change in an electronic prescribing system as a potential source of information for drug safety and effectiveness.

Objectives: To determine the accuracy of an electronic prescribing and drug management system in documenting orders for discontinuation and dose changes of prescription drug treatment, and in identifying the reasons for the drug discontinuation and dose change.

Study design and setting: We prospectively assessed the accuracy of electronic prescription orders for drug discontinuation and dose change by comparing them with treatment changes documented by physician-facilitated medical chart review (gold standard). Validity was evaluated in 620 patients of 22 community-based primary care physicians in addition to the reasons for these treatment changes.

Results: A total of 141 (41.7%) drug discontinuation orders and 197 (58.3%) changes in drug doses were identified by chart review, the majority of which were for cardiovascular and CNS drugs. Ineffective treatment (30.8%), adjusting dose to optimize treatment (25.1%) and adverse drug reactions (21.9%) were the most common reasons for treatment change. The sensitivity of the electronic prescribing system in identifying physician-initiated drug discontinuations and dose changes was 67.0% (95% CI 54.1, 77.7) and the specificity was 99.7% (95% CI 99.5, 99.9). The positive and negative predictive values of electronic treatment discontinuation and change orders were 97.3% (95% CI 95.6, 98.7) and 95.8% (95% CI 92.9, 97.7), respectively.

Conclusion: An electronic prescribing and drug management system documents drug discontinuation and dose-change orders with high specificity and moderate sensitivity. Ineffective treatment, dose optimization and adverse drug reactions were the most common reasons for drug discontinuation or dose changes. The electronic prescribing system offers a new method for augmenting pharmacosurveillance.

Background

In the US, adverse drug events are among the leading causes of death,[1] at an annual cost of more than $US177 billion dollars.[2] Postmarketing surveillance is crucial to quantify previously recognized adverse drug reactions, to identify unrecognized adverse drug events, to evaluate the effectiveness of the drugs in real-world situations[3] and to decrease mortality and morbidity associated with adverse drug events.

Although evidence supporting the safety and effectiveness of drugs is required before a drug is approved, the data typically come from randomized controlled trials conducted with a limited number of patients who are selected carefully to optimize compliance and limit co-morbidity.[4-6] This population of patients often does not represent the typical patient treated with the drug after its approval. Moreover, the use of surrogate endpoints (e.g. changes in weight or blood sugar level) may not confer expected benefits for clinically relevant long-term outcomes (e.g. stroke, myocardial infarction, mortality).[7] Challenges in the evaluation of medication safety and effectiveness are compounded when drugs are used off-label. Off-label prescribing is estimated to occur in one-third of prescriptions.[8,9] As a result, there may be different effectiveness and safety profiles of drugs in the postmarket patient population.

The Need for New and Innovative Pharmacosurveillance Methods

Spontaneous reporting has been a successful method of identifying some serious adverse drug events within months of the approval of a new drug.[10,11] However, known limitations of spontaneous reporting include systematic under-reporting (estimated to be in the range of 90–98%[6,12-14]), lack of denominators to estimate incidence and delays in detection.[6,14] Prescription event monitoring (PEM) is a more recently developed method for pharmacosurveillance that requires physicians to respond to a follow-up questionnaire on patients' responses to new drugs[15] while making no cause-effect association between the drug and the adverse drug event. PEM has an average response rate of 53% (range 35–65%); however, when more than 30 patient questionnaires are sent to a single physician, only 28% of physicians respond.[15,16] The labour-intensive nature of data collection makes the method unsustainable for a nation-wide surveillance,[17] which is essential to detect adverse drug events rapidly. Neither spontaneous reporting nor PEM are aligned to the day-to-day activities of physicians, especially primary care physicians, who are responsible for the majority of prescriptions written.[18]

Lessons may be forthcoming from public health. Efforts to engage front-line practitioners in mandatory disease reporting as a front-line surveillance tool have been replaced or supplemented with electronic surveillance through the secondary use of electronic 'point-of-care' information systems. Laboratory, pharmacy, population health information centres and emergency department triage and treatment systems are mined to identify notifiable diseases, symptom clusters and emerging epidemics.[19,20] There is an opportunity to use a similar strategy in pharmacosurveillance that addresses the current problems of under-reporting of adverse drug events and lack of timely data without adding to physicians' practice burden.

Electronic Prescribing and Drug Management Systems

A common area of focus in Canada, Europe, Australia, New Zealand and the US is the implementation of electronic prescribing and integrated drug management systems. This is because it is widely accepted that computerization of drug management will reduce avoidable errors in prescribing and dispensing.[21-24] Primary care physicians in Denmark, the UK and New Zealand are leaders in electronic prescribing, with >90% of prescriptions written electronically.[25,26] Although the US and Canada have lagged behind other nations in the adoption of electronic prescribing,[18,26] new regional and national investment initiatives should rectify this situation.[27]

Transmission of orders to dispensing pharmacies to discontinue medication and monitoring of patient

treatment outcomes, two features of computerized prescribing systems, are considered to be important factors in improving the safety and effectiveness of drugs.[21,28] Reasons for discontinuing or changing a dose of a medication could be added as a mandatory field to electronic drug discontinuation orders. This information could be used to augment the detection of potential adverse events in conjunction with spontaneous adverse drug event reporting systems and PEM.[29-31] Requiring physicians who utilize electronic prescribing to enter reasons for drug discontinuation or dose changes, such as adverse drug reaction or ineffective treatment, could enable such data to be rapidly collected and analysed systematically as part of a pharmacosurveillance system. These data could be used by regulatory agencies to estimate the incidence of potential adverse drug events and ineffective treatments, and to compare the rates of adverse events associated with different drugs in real-world patient populations. The development and standardization of these methods nationally and internationally could greatly increase the data available to signal potential efficacy and safety problems early in the postmarketing phase and may lead to a more thorough and directed investigation of the drugs involved.

Objectives

The feasibility of such a method of treatment outcome monitoring and the validity of the information generated by electronic prescribing systems has not been investigated. The aims of this study were to determine the accuracy of an electronic prescribing and drug management system in: (i) documenting orders for drug discontinuation and dose changes of prescription drug treatment; and (ii) identifying the reasons for the drug discontinuation and dose change of medications.

Context

An integrated electronic prescribing and drug management system (Medical Office for the XXI century [MOXXI]) was developed by the clinical and health informatics research group at McGill University, in Montreal, Quebec, Canada, and implemented in a population of primary care physicians (family physicians) to study the effects of computerized systems in primary care.[32] Similar to other electronic prescribing systems,[33] physicians can document a patient's drug, disease and allergy profile and write and transmit prescriptions. Through interfaces with pharmacy and provincial insurance systems, physicians using MOXXI can retrieve information on recent emergency department visits and hospitalizations, all dispensed prescriptions and all health problems identified in medical services claims by themselves and other physicians. Additional features of MOXXI include preloading and integration of patient demographic information, automated alerts for potential drug interactions and drug disease and allergy contraindications.

Physicians using the MOXXI system can order the discontinuation of a drug or change a dose; this information is sent electronically to the dispensing pharmacy and is printed on the prescription (figure 1). Reasons for drug discontinuation or change in dose must be completed for each treatment change order. Physicians select from a menu of standard options including adverse drug reaction, ineffective treatment, drug interactions, adjusting dose to optimize treatment, error in prescribing, incorrect medication dispensed, end of treatment, simplifying treatment, substitution for less expensive drug and temporary discontinuation.

Physicians were eligible for inclusion in the MOXXI research programme if they practiced in selected geographical locations in Montreal and Quebec City, were remunerated on a fee-for-service basis (approximately 85% of Quebec physicians), and worked in office-based practice three or more days per week. Overall, 410 physicians met the criteria for inclusion in the study, and 104 (25%) of these consented to participate. On average, participating physicians were 5 years younger than non-participating physicians. The mean rate of electronic prescribing was 36.9 prescriptions per 100 visits (interquartile range: 14.0; 45.0) in the first 20 months post-implementation.[32] Physicians were more likely to use the system for patients who had

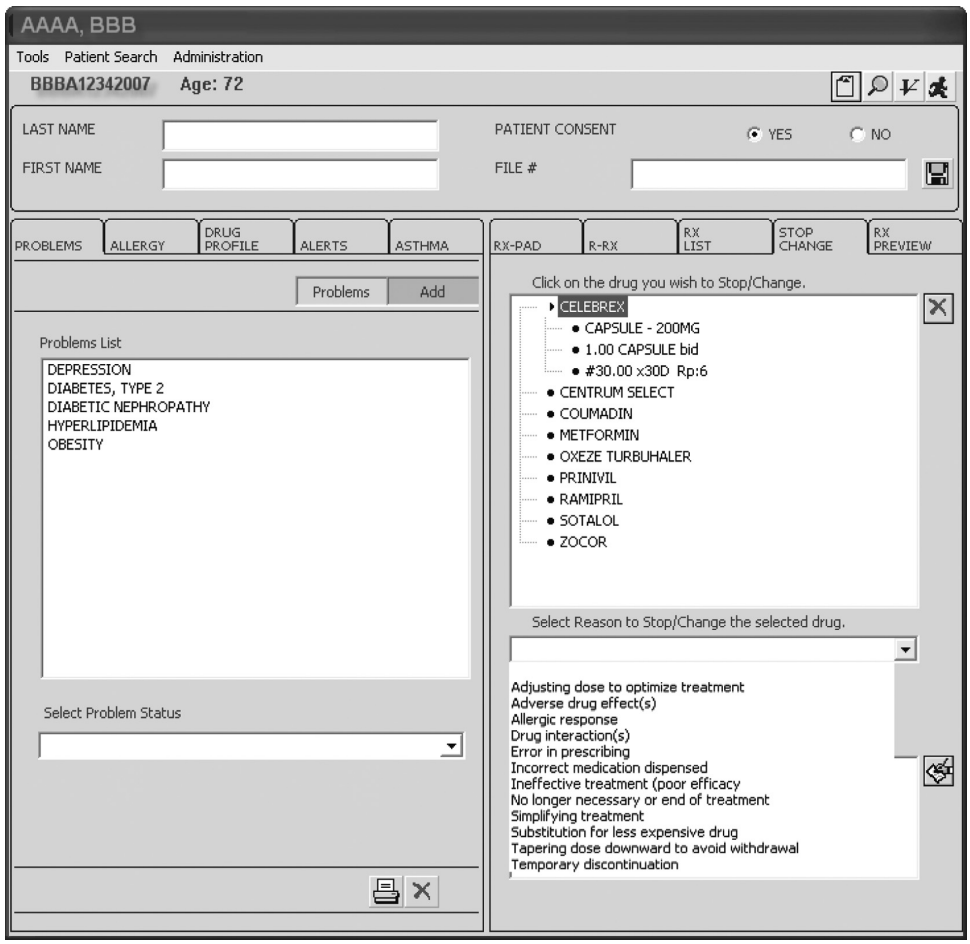

Fig. 1. Drug discontinuation and dose-change feature of the Medical Office for the XXI century prescribing and drug management system.

more complex drug therapy, higher fragmentation of care, more emergency department visits and a greater number of prescribing physicians.[34,35]

Methods

The accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the MOXXI system in documenting prescription drug discontinuation and dose-change orders was assessed by comparing information obtained from the MOXXI system with information from physician-facilitated chart review. The sensitivity provided an estimate of the extent to which all treatment changes for the targeted drugs were recorded by the computerized prescribing system whereas the specificity provided an estimate of the extent to which physicians would erroneously record treatment changes that had not occurred.

Design and Study Population

The study was conducted in the 22 physicians of the 104 enrolled who had more experience in the use of MOXXI electronic prescribing system, in order to ensure that the validity of treatment change orders would not be confounded by differences in physician experience using the MOXXI system. Patients were eligible for this study if they had made a visit to a study physician between 5 December 2005 and

30 March 2006 and had received an electronic prescription for a chronic condition. Medications prescribed for episodic conditions (anti-infectives, ear, eye, nose and throat drugs, skin and mucous membrane preparations and vitamins) and drugs with frequent changes in dose (anticoagulants) were not eligible because these drugs are supplied for a limited time and most anticoagulant dose changes occur by telephone without the patient visiting a physician.

Assessment of Drug Discontinuation and Dose-Change Orders within the Electronic Prescribing System

All patients with an electronic drug discontinuation or dose-change order during the study period were included. An equivalent number of patients without treatment change orders were randomly sampled for each physician on each day that treatment change orders were documented. To improve study efficiency, a one-to-one sampling ratio between treatment change order positive and negative visits was used.[36] The sample size was calculated using an estimated sensitivity of 75% and an incidence rate of treatment change of 8 per 100 electronic prescriptions. To obtain a 95% confidence interval for sensitivity within 10% of the true value, we calculated that we would need a sample size of 600 visits with 300 treatment change positive visits and 300 treatment change-negative visits. An automated database query was developed to identify, on a daily basis, the patients with a treatment change-positive visit for eligible drugs. For each treatment-change positive visit, we developed another query to sample one treatment change-negative visit for the same physician that occurred on the same day of each treatment change-positive visit.

Gold Standard: Physician-Facilitated Chart Review

One of the challenges in conducting chart review in primary care is that the documentation is typically not as extensive as hospital charts. As much as 10% of diagnostic and treatment decisions and 70% of patient education is not recorded in the primary care medical chart.[37] To address this problem, an interview with the physician was carried out within 24 hours of the patient's visit by two healthcare professionals after training and standardization. During the interview a chart review was carried out. By using this approach, we increased the likelihood that the physician was able to recall undocumented details of the patient situation, thereby providing a more complete assessment of treatment changes. The automated database query that flags a drug discontinuation or dose change was used to identify patients in whom a treatment change had occurred. Sampled patients' visits were identified by the physician's name, patient's name, age, sex, unique identifier, visit date and time. Interviewers were blinded to treatment change status and the reasons for treatment change.

The interviews were carried out each time a patient pair (one treatment change-positive visit; one treatment change-negative visit) was identified. The interviewers arranged with the physician's receptionist for the patient's medical charts to be available to the physician during the interview process and an interview for the pair carried out at the same time. Neither the physicians nor the interviewers were allowed to open the MOXXI application at the time of the interview. A structured questionnaire was used to determine if a patient had had a drug discontinuation or a dose change. With each treatment change reported by the physician, the reason for the treatment change was requested and spontaneous responses were documented. The physician was then asked to identify which of the reasons listed in the application (e.g. adverse drug reaction, ineffective treatment, adjusted dose to optimize treatment) was the main reason for the treatment change. Interview data were entered into a computerized database and later linked to the MOXXI data file with treatment change status.

Data Analysis

Sensitivity, specificity, PPV and NPV of electronic drug discontinuation and dose-change orders were estimated. Sensitivity was defined as the proportion of actual treatment change-positive visits documented in physician-facilitated chart review

that were correctly identified by the MOXXI electronic prescribing system. Specificity was defined as the proportion of actual treatment change-negative visits that were correctly identified by the MOXXI electronic prescribing system. Naive sensitivity and specificity that are uncorrected for sampling fraction of patients with and without a treatment change order were calculated. These estimates were then corrected to address the over-sampling of treatment change-positive orders and avoid verification bias (overestimation of sensitivity and underestimation of specificity). The sensitivity and specificity measures were corrected using the prevalence of treatment change orders in the MOXXI system during the study period using the formula for sensitivity:[36]

$$\frac{a}{a + c(w/(1-w))(p-/p+)} \quad \text{(Eq. 1)}$$

where w = the proportion of the sample with treatment change (MOXXI positive), 1 − w = the proportion of the sample with no treatment change (MOXXI negative), p+ = the proportion of treatment change orders in the MOXXI system (population), p− = the proportion of orders with no treatment change in the MOXXI system (population), a = the number of MOXXI-positive records, which are identified by chart review as having treatment change (true positives) and c = number of MOXXI-negative records, which are identified by chart review as having treatment change (false negatives). Adjustment for verification bias was done by multiplying the treatment change-positive and -negative groups by the inverse of the selection probability. In general, adjustment for verification bias results in a decrease in the sensitivity and an increase in the specificity measures.[38] 95% CIs were constructed using the logit method of Begg and Greenes[38] and Pepe.[39] Multivariate logistic regression with a generalized estimating equation framework was used to determine if there were significant differences in the demographic and clinical characteristics of patients with and without a treatment change order. The physician was the clustering factor and an independent correlation structure was specified with robust standard error.[40]

Ethics

The MOXXI research programme on electronic prescribing and drug management in primary care was approved by the provincial privacy commission, the legal counsel of the provincial health insurance agency, the Quebec College of Physicians and the McGill University, Faculty of Medicine Institutional Review Board. All patients and physicians are consented to be part of the research programme.

Results

In the period from 5 December 2005 to 30 March 2006, there were 17 696 drugs prescribed electronically by study the physicians. Among all electronic prescriptions, 1435 (8.11%) were discontinued or the dose was changed using the treatment change feature in the MOXXI system. A total of 620 patients (310 with treatment change order and 310 patients without a treatment change order) were included in the study. Patients with treatment change orders were taking more medications than patients without treatment change orders and were more likely to have a diagnosis of hypertension, depression and insomnia (table I).

Table I. The characteristics of patients who had drug orders for discontinuation and dose changes vs no change in drug treatment (no order for discontinuation or dose change)

Status of treatment change by electronic treatment documentation			
patient characteristics	yes (n = 310)	no (n = 310)	p-value[a]
Age in years [mean (median)]	57.6 (60)	55.6 (57)	0.506
Number of drugs [mean (median)]	4.0 (6)	2.6 (4)	0.0003
Number of medical problems [mean (median)]	8.3 (9)	7.3 (6)	0.125
Female [n (%)]	193 (62.3)	201 (64.8)	0.576
Prevalent medical problems [n (%)]			
hypertension	110 (35.6)	75 (24.1)	0.001
hyperlipidaemia	65 (20.9)	47 (15.2)	0.519
hypothyroidism	39 (12.4)	34 (11.1)	0.579
depression	44 (14.2)	24 (7.7)	0.031
insomnia	41 (13.1)	21 (6.9)	0.023

a Multivariate logistic regression under generalized estimating equation framework with physician as a clustering variable.

Table II. Reasons for treatment changes of drug identified by physician-facilitated chart review

Summary reasons	Total [n (%)]	Dose change [n (%)]	Drug discontinued [n (%)]
Ineffective treatment	104 (30.8)	62 (31.5)	42 (29.8)
Adjusting dose to optimize treatment	85 (25.1)	85 (43.2)	0
Adverse drug reaction(s)	74 (21.9)	13 (6.6)	61 (43.3)
Error in prescribing	20 (5.9)	15 (7.6)	5 (3.6)
No longer necessary or end of treatment	17 (5.0)	1 (0.5)	16 (11.4)
Tapering dose downward to avoid withdrawal	15 (4.4)	15 (7.6)	0
Simplifying treatment	12 (3.5)	3 (1.5)	9 (6.4)
Substitution for less expensive drug	5 (1.5)	2 (1.0)	3 (2.1)
Drug interaction(s)	2 (0.6)	0	2 (1.4)
Incorrect medication dispensed	2 (0.6)	1 (0.5)	1 (0.7)
Temporary discontinuation	2 (0.6)	0	2 (1.4)
Total	338	197 (58.3)	141 (41.7)

Drug discontinuation orders accounted for 41.7% of all treatment changes in drug therapy and the remainder was dose changes. Ineffective treatment (30.8%), adjusting dose to optimize treatment (25.1%) and adverse drug reactions (21.9%) were the most common reasons for changing drug treatment (table II). Drugs were discontinued most often because of adverse drug reactions (43.3%) and ineffective treatment (29.8%). Most dose changes were increases in dose (70.8%) to optimize treatment (43.2%) or because treatment was ineffective (31.5%) [table II].

The majority of treatment change orders were for cardiovascular drugs (33.4%), CNS drugs (32%) and hormone and synthetic substitutes (19.8%) [figure 2]. Most cardiovascular drugs were anti-hypertensive (56.6%), followed by anti-lipaemic agents (23%) and cardiac drugs (20.4%). Among the CNS drugs, treatment change orders were predominantly for antidepressants or antipsychotic drugs (59.2%). Ineffective treatment was the reason for treatment changes in 35.3% of cardiovascular drugs, 24.1% of CNS drugs and 73.7% drugs acting on the gastrointestinal system. Adverse drug reactions were responsible for treatment changes in 23% of cardiovascular drugs, 19.4% of central nervous system drugs and 26.8% of hormone and synthetic substitutes. Drugs that were most frequently discontinued or modified were levothyroxine sodium (14/73), amlodipine (13/62) and metformin (12/63) [table III]. Adverse drug reactions reported included aching of muscle and numbness (atorvastatin) and dysphagia and dyspepsia (alendronate) [table IV].

The sensitivity of the MOXXI application in identifying actual treatment changes of drugs was 96.2% and the specificity was 97.1% (figure 3). When the sensitivity and specificity were corrected for the sampling fraction,[38,39] the corrected sensitivity was 67.0% (95% CI 54.1, 77.7) and the corrected specificity was 99.7% (95% CI 99.5, 99.9) [figure 3]. The unbiased PPV was 97.3% (95% CI 95.6, 98.7) and the unbiased NPV was 95.8% (95% CI 92.9, 97.7).

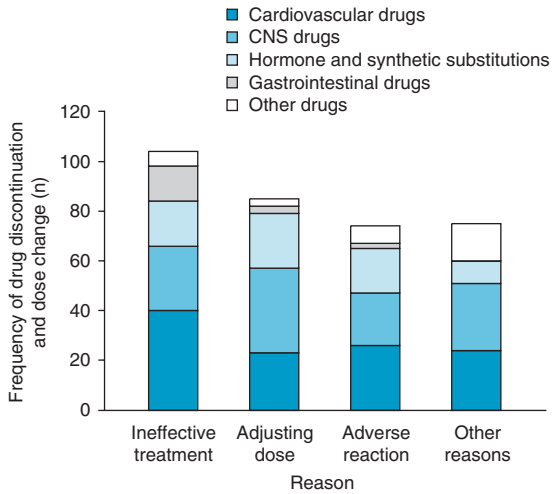

Fig. 2. Frequency distribution of drug discontinuation and dose change by drug class and by the reason for discontinuation or change.

Table III. Drugs most frequently discontinued or the dose changed

Drug[a]	Therapy change	Dose change	Drug discontinued
Synthroid® (levothyroxine)	14	13	1
Norvasc® (amlodipine)	13	8	5
Metformin	12	11	1
Effexor® (venlafaxine)	11	9	2
Celexa® (citalopram)	9	6	3
Lipitor® (atorvastatin)	8	3	5
Hydrochlorothiazide	8	4	4
Pantoloc® (pantoprazole)	7	1	6
Diovan® (valsartan)	7	4	3
Elavil® (amitriptyline)	7	5	2
Wellbutrin® (bupropion)	5	3	2

a The use of trade names is for identification purposes only.

The concordance between the reasons for drug discontinuation and dose change documented by the MOXXI application and the actual reasons reported in physician-facilitated chart review was 95.2% for ineffective treatment, 85.7% for adverse drug reaction and 80.8% for adjusting dose to optimize treatment (figure 4). The PPV of the MOXXI application for identifying adverse drug reactions was 85.7%, while ineffective treatment and adjusting dose to optimize treatment had PPVs of 84.6% and 87.5%, respectively.

Discussion

We assessed the accuracy of drug discontinuation and dose-change orders documented in an electronic prescribing and drug management system to determine if this information could be used to identify physician-identified adverse drug events and other drug-treatment outcomes. We found that physicians' drug discontinuation and dose-change orders can be recorded with excellent accuracy as can the reasons for the discontinuations and changes.

Concordance in reasons for treatment changes between the electronic prescribing system and the chart review was from 80.8% to 95.2% and could be improved by reducing the conceptual overlap of reasons for treatment changes. For example, a physician may indicate that a treatment was ineffective at a given dose and increase the dose to achieve the desired effect. In this case, both 'ineffective treatment' at the current dose and 'adjusting dose to optimize treatment' are accurate reasons for the physician's action. The creation of mutually exclusive categories and separate lists of reasons for dose changes and for drug discontinuations are two solutions that should address this problem. Moreover, the sensitivity of electronic prescribing systems could be improved with regulatory requirements for electronic prescribing, increased familiarity with the application and use of drug discontinuation and dose-change features for all patients.

Blinding of the interviewers and the physicians as to the treatment change status of the patients' in the electronic prescribing system is one of the strong features of the study and helps to control observer bias and diagnosis review bias, respectively and provides unbiased results. The administration of physician-facilitated chart review soon after patients' visits is another strong feature that helps to decrease recall bias from the physicians.

Table IV. The most frequently discontinued drugs with the adverse drug reactions reported as reasons for discontinuation

Drug[a]	Adverse drug reactions (number of patients)
Lipitor® (atorvastatin)	Aching of muscles (2)
	Aching and numbness (1)
	Dizziness (1)
Fosamax® (alendronate)	Dysphagia and odynophagia (1)
	Dyspepsia (1)
Mevacor® (lovastatin)	Elevated liver enzymes (2)
Norvasc® (amlodipine)	Dizziness (1)
	Excessive fatigue (1)
	Leg swelling (1)
	Severe constipation (1)
Elavil® (amitriptyline)	Generalized itching (1)
	Drowsiness (1)
Ramipril	Cough (1)
Avandia® (rosiglitazone)	Weight loss and diarrhoea (1)
Celexa® (celexa)	Somnolence (1)
	Sleepiness and drowsiness (1)
Metformin	Diarrhoea (2)
	Nausea and upset stomach (1)
Effexor® (venlafaxine)	Insomnia (1)
Diovan® (valsartan)	Cough (1)
	Low potassium level (1)
	Dizziness and hypotension (1)

a The use of trade names is for identification purposes only.

		Chart review		
		Treatment change positive	Treatment change negative	Total
Electronic prescribing system documentation	Treatment change positives (MOXXI positives)[1]	325	9	334
	Treatment change negatives (MOXXI negatives)[2]	13	298	311
	Total	338	307	645[3]

Measures	Naive estimates	Corrected estimates (95% CI)[4]
Sensitivity	96.2	67.0 (54.1, 77.7)
Specificity	97.1	99.7 (99.5, 99.9)

Fig. 3. Sensitivity and specificity of treatment change orders in the Medical Office for the XXI century (MOXXI) electronic and prescribing system compared with physician-facilitated chart review (gold standard). **1** Treatment change orders in the MOXXI system during patient's visit; **2** Prescription orders where there is no treatment change order during patient's visit in the MOXXI system; **3** There were a total of 25 visits where two treatment change orders occurred in one patient's visit; **4** Corrected using the prevalence of treatment change orders in the MOXXI system (8.11%) during the study period with the method of Begg and Greenes[38] and Pepe.[39]

Early introduction of computerized dispensing has paved the way for successful implementation of PEM in UK and New Zealand.[17,41] Advances in electronic prescribing systems and electronic health records are enabling real-time collection of data on drugs and patients and creating an opportunity to evaluate the effectiveness and safety of drugs in a timely and unbiased manner. Electronic prescribing and data exchange by primary care physicians is widely adopted in Denmark and New Zealand. Although not all electronic prescribing systems provide mandatory documentation of treatment indication, or reasons for drug discontinuation and dose change, these features can be readily incorporated into existing systems. Electronic prescribing vendors and users have demonstrated the willingness and creativity to include new features in electronic prescribing systems.[33,41] Furthermore, as standards and financing of computerization of health care are primarily determined by national and regional health authorities, certification processes for required features are already in place. The addition of the rationale for treatment change orders could be readily included as a required feature for certification. Our study suggests there may be a substantial benefit in doing so. We showed that an electronic prescribing system can accurately document physician-identified adverse drug events better than spontaneous reporting system[42] and can be easily integrated into clinical work flow. Broad scale adoption of electronic prescribing nationally and internationally is critical, both to detect rare events and also to minimize potential bias resulting from selective participation that may occur in both standard, and new forms of pharmacosurveillance. A pharmacosurveillance tool needs a sample size in the range of from 10 000 to 100 000 person-years of observations to detect rare adverse drug events, which occur 3 in 10 000 and 3 in 100 000, respectively,[43,44] and these sample sizes can be attained in a relatively short period of time if electronic prescribing becomes legally mandated (Denmark)[45] or voluntarily introduced by legislative means such as with the US Medicare Reform Bill.[46]

One limitation of the study is that physicians were aware of the close monitoring of their behaviours during the study period. This could have resulted in a possible increase in the sensitivity of the

		Reason documented in MOXXI system				
		Adjusting dose to optimize treatment	Adverse drug reaction(s)	Ineffective treatment	Other reasons[1]	Total
Reason from physician interview	Adjusting dose to optimize treatment	63	3	6	6	78
	Adverse drug reaction(s)	1	60	6	3	70
	Ineffective treatment	3	1	99	0	103
	Other reasons[1]	5	6	6	57	74
	Total	72	70	117	66	325

Fig. 4. Concordance in reason for treatment change orders from electronic prescribing system in comparison to physician-facilitated chart review. **1** To simplify the table, other reasons (error in prescribing, no longer necessary or end of treatment, tapering dose downward to avoid withdrawal, simplifying treatment, substitution for less expensive drug, drug interaction, incorrect medication dispensed and temporary discontinuation) were aggregated together. Drug interaction refers to the modification of a drug combination that may increase the risk of adverse event. If an adverse event (e.g. bleeding) did occur due to drug interactions, it would be recorded as an adverse event.

system if they recorded more treatment changes during the study. However, the treatment change rate changed by <0.11% during the study period. In addition, the treatment change feature is considered to be an important feature by the physicians in clinical decision making because drugs discontinued or changed are included as part of the prescription. Medications prescribed for episodic conditions (e.g. anti-infective agents) may not be readily monitored through computerized prescribing systems since these drugs are supplied for a limited time and many treatment changes take place by telephone call-back to the physician or pharmacist. However, alternative approaches such as pharmacy call-back programmes, which are increasingly popular in community-based pharmacies, may provide a follow-up service for new prescriptions that could fill this gap.[47] Electronic treatment change orders will also not capture severe reactions and deaths. Yet, if electronic prescribing systems could be combined with administrative data to determine mortality and hospital admissions, a more sensitive and comprehensive pharmacosurveillance system may be possible. Currently, an international effort to automate mortality statistics is underway to speed up registration of deaths and the availability of death data.[48] Future studies should evaluate the added benefit of using electronic prescribing information linked with administrative data as a pharmacosurveillance tool. Although our findings can not be extrapolated to all physicians, they may be generalized to clinical settings where electronic prescribing is mandatory and where physicians are well versed in using computerized prescribing system.

Timely data on the safety and effectiveness of drugs will enable regulatory bodies to evaluate drugs objectively, and identify drugs with suboptimal safety and effectiveness profiles in practice, and avoid unwarranted withdrawals of drugs on the basis of sporadic and incomplete evidence. Researchers, drug regulatory bodies and the pharmaceutical industry should work together in shaping future directions of computerized prescribing systems to enable new opportunities for pharmacosurveillance.

Conclusion

Validation of an electronic prescribing and drug management system that documents drug discontinuation and dose-change orders showed high specificity and moderate sensitivity. The electronic prescribing system offers new method for augmenting pharmacosurveillance. Our results provide strong evidence to support incorporating drug discontinuation and dose-change orders as a required feature in

integrated electronic prescribing systems to augment prescription event monitoring and spontaneous drug event reporting systems in signalling potential drug-related problems to target priorities for safety and effectiveness evaluations.

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SHORT COMMUNICATION

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Enhancing Pharmacosurveillance with Systematic Collection of Treatment Indication in Electronic Prescribing

A Validation Study in Canada

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Abstract

Background: Adverse drug reaction reports used in pharmacosurveillance often lack complete information on treatment indication that is important for benefit-risk analyses and clinical and regulatory decision making. A systematic documentation of treatment indication using electronic prescribing applications provides an opportunity to develop new pharmacosurveillance tools that will allow evaluation of drugs by weighing benefits and risks for specific indications, and evaluate off-label prescribing. In addition, interfacing indications with reminders and clinical guidelines can enhance clinical decision making. We investigated the validity of treatment indications documented using an electronic prescribing system at the time of prescribing.
Objectives: To determine the sensitivity and positive predictive value (PPV) of an electronic prescribing system in documenting treatment indications at the time of drug prescribing, and to investigate the use of treatment indication data to evaluate off-label prescribing in primary-care practice.
Study Design and Setting: We prospectively assessed the validity of documenting treatment indication using an electronic prescribing system by comparing it with treatment indications documented by physician-facilitated medical chart review ('gold standard'). Sensitivity and PPV were evaluated in 338 patients of 22 community-based primary-care physicians in Quebec, Canada, in 2006.
Results: The sensitivity of the electronic prescribing system in documenting treatment indication was 98.5% (95% CI 96.5, 99.5) and the PPV of the system in accurately identifying the treatment indication was 97.0% (95% CI 94.2, 98.6). The treatment indication data collected using this system allowed assessment of off-label prescribing.

Conclusions: The electronic prescribing system offers a valid method for documenting treatment indication at the time of prescribing. Our results provide strong evidence to support incorporating mandatory recording of treatment indication in integrated electronic prescribing systems to provide a critical piece of information for the evaluation of safety and effectiveness of drugs.

Background

Current pharmacosurveillance methods are slow and inadequate in addressing critical questions of drug safety and effectiveness.[1,2] These methods are plagued by high rates of underreporting of adverse drug reactions (ADRs),[2] including fatal ADRs.[3] They also lack important clinical variables such as indication for treatment, risk factors (e.g. smoking, alcohol consumption), physical examination and laboratory indices (e.g. blood pressure, weight, glycosylated haemoglobin [HbA_{1c}]) and health outcomes (quality of life, functional status) that provide essential context for making rigorous safety and effectiveness decisions. In particular, the lack of information on treatment indication means that drugs are not evaluated in terms of their risks and benefits for a specific disease entity, but instead for all disease conditions where the drug may be prescribed.[4-6]

Mandatory documentation of treatment indication at the time of prescription has several potential advantages, including the opportunity to generate diagnosis-based reminders for drug selection and follow-up, to incorporate clinical guidelines into the decision process, provide pharmacists with critical information for safe dispensing of drugs and appropriate patient counselling[7,8] and to create longitudinal drug treatment history (e.g. treatment failures by indication and their reasons). It will also enhance capacity for new automated pharmacosurveillance methods to be developed that assesses safety and effectiveness of drugs by treatment indication. Moreover, using such data will allow evaluation of the magnitude of off-label prescribing and its determinants with the associated safety and economic implications.

The feasibility of using electronic prescribing applications to retrieve treatment indication for prescribed medications through mandatory documentation and the validity of documentation at the time of prescribing has not been investigated. The aims of this study were to (i) determine the sensitivity and positive predictive value (PPV) of using an electronic prescribing system to document treatment indications at the time of prescribing; and (ii) investigate the use of treatment indication data to evaluate on- and off-label prescribing in primary-care practice.

Methods

Context

An integrated electronic prescribing and drug management system (Medical Office for the XXI century [MOXXI]) was developed by the Clinical and Health Informatics Research Group at McGill University and implemented in a population of primary-care physicians to study the effects of computerized systems in primary care in the province of Quebec, Canada.[9] Similar to other electronic prescribing systems,[10] physicians can document a patient's drug, disease and allergy profile, and write and transmit prescriptions electronically. Through interfaces with the provincial insurance system, MOXXI physicians can retrieve data describing recent emergency department visits, hospitalizations, dispensed prescriptions and health problems identified in medical services claims. All of these data are preloaded and integrated with patient demographic information, allowing the generation of automated alerts for potential drug-drug and drug-disease interactions or allergy contraindications. MOXXI physicians can order the

discontinuation of a drug or change a dose. Reasons for these therapy changes are captured and the prescription can be sent either electronically or manually to the pharmacy. This drug discontinuation and dose-change feature was validated by chart review and found to have high specificity and PPV and moderate sensitivity.[11]

One important feature of the MOXXI prescribing system is a mandatory requirement for physicians to select at least one treatment indication for each prescribed drug from a list of approved (on-label) indications and unapproved (off-label) indications. Treatment indications are specific to each drug and can be selected from a drop-down menu or entered manually using free-text entry (figure 1). The purpose of entering treatment indication is to document, in standard format, data that are used to populate the patient's health problem list. Entering the treatment indication at the time of prescribing will also be used to provide computerized decision-support for drug-disease interactions and chronic disease management. Physicians can change the status of a particular health problem(s) to inactive, excluding those from the drug-disease interaction monitoring after the problems are resolved or successfully treated. Currently, there are 2540 unique drugs and 1249 unique treatment indications in the system. The list of drugs and therapeutic indications for a drug is updated monthly through ongoing review of drug monographs, compendia and published studies.[12]

Design and Study Population

Physicians were eligible for inclusion in the MOXXI research programme if they practiced in Montreal, were remunerated on a fee-for-service basis (approximately 85% of Quebec physicians) and worked in an office-based practice for 3 or more days per week. Overall, 410 physicians met these criteria, of whom 104 (25%) consented to participate.[9] The study was conducted among 22 physicians who had 2 years experience using the MOXXI electronic prescribing system. Since the aim of this study was to evaluate the routine capture of treatment indication using an electronic prescriber, we excluded recently trained physicians to ensure that the validity of treatment indication

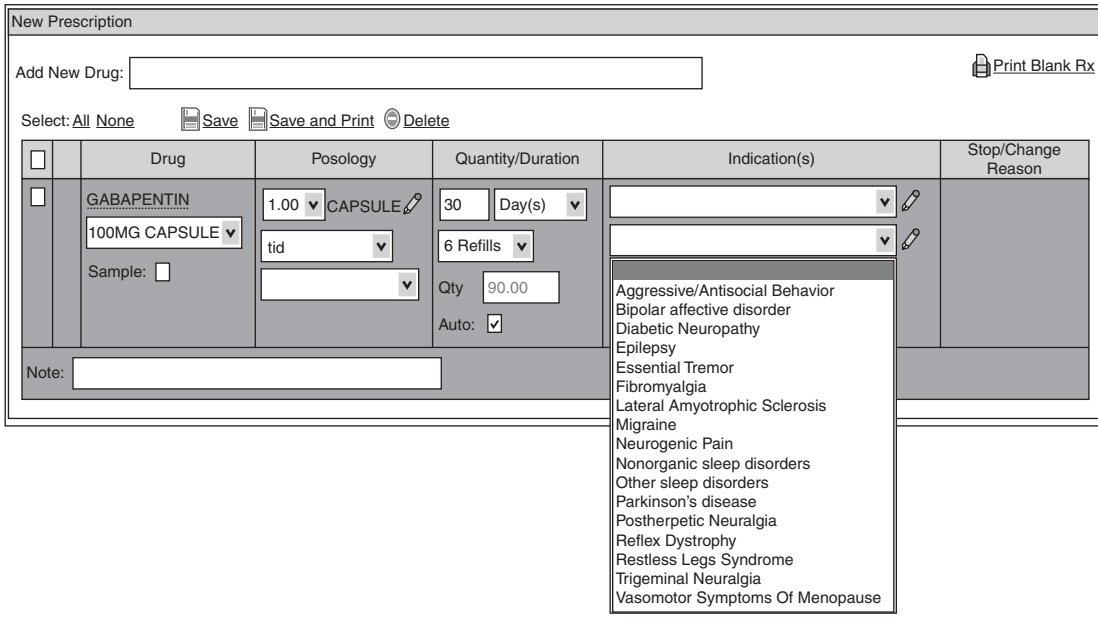

Fig. 1. Documentation of treatment indication in the Medical Office for the XXI century (MOXXI) system.

documentation was not confounded by differences in physician experience with the system.

Patients were eligible for this study if they had made a visit to a study physician and received an electronic prescription. We first sampled work-days for a particular physician, taking into account the number of days the physician was working and the availability of the physician for an interview. Whenever the physician could not be contacted within 24 hours, the particular prescription was replaced by another patient visit to the same physician. Three hundred and thirty-eight visits made by consenting patients in the year 2006 were used to ascertain whether the treatment indication recorded by MOXXI was an accurate representation of the physician's intent documented in the patient chart. Health Canada's drug product database was used to identify on- and off-label indications for each drug.[13]

Physician-Facilitated Chart Review

One of the challenges in determining treatment indication is that health problems and treatments are documented but rarely explicitly linked. Moreover, as much as 10% of diagnostic and treatment decisions and 70% of patient education activities are not recorded in the primary-care medical chart.[14] To address these two challenges, we conducted a physician-facilitated chart review by telephone ('gold standard') within 24 hours of the patient visit, to link drugs and indications and increase the likelihood that the physician was able to recall undocumented details of the patient visit.

Records of patients' visits included physician name, patient name, age, sex, unique visit identifier, visit date and time. Prior to the interview, the receptionist or the nurse was contacted to retrieve the respective charts. The interviewer confirmed that the physician had the chart available for reference before starting the chart review interview. Treatment indication for a specific patient and drug was obtained from the physician with an open-ended request: ''identify and describe the treatment indication for the drug you prescribed for this patient.'' All treatment indications provided by the physician for a given drug were coded as matching (yes/no) to the treatment indications recorded in the MOXXI database.

In reviewing the patient chart, physicians were not allowed to open the MOXXI application during the interview so that they were not reminded what indication they had selected. Interviewers were also blinded about the treatment indication selected by the physician at the time of prescribing for a particular patient. Physician interviews were conducted by two health professionals after training and standardization. Interview data were entered into a computerized database and later linked to the data file with treatment indication.

Data Analysis

Characteristics of the patient population and treatment indications were summarized using descriptive statistics. In data accuracy studies from computerized systems,[15-18] two complimentary measures, the sensitivity and the PPV, provide answers to the two most important questions: the completeness and the correctness of the information captured by the electronic system, respectively. In our study, sensitivity was defined as the proportion of treatment indications documented in the chart that were correctly identified by the electronic prescribing system. PPV was defined as the proportion of treatment indications documented in the electronic system that were found to be correct by chart review. 95% confidence intervals (CIs) were constructed using the exact method for binomial proportions.[19] The design of most research that assesses data accuracy does not allow the true negatives to be assessed. This is because true negatives may be infinitely large[16] (e.g. persons without hypertension or systemic lupus erythematosus). In our study, the true negatives represent the number of treatment indications that were not recorded by the electronic prescriber that should not have been recorded in the chart of the patient as well.

The discordance between the chart and electronic prescription documentation of treatment indication was analysed qualitatively to assess the

nature of differences in indications recorded. In addition, each drug/indication combination was classified as on- or off-label using Health Canada drug approvals, and then the proportion of off-label prescribing was estimated.

Results

Among the 338 patients who made a visit in the study period, the average age was 58.2 years (median 60), 62.1% were females and, on average, patients had 8.3 medical problems (median 9) and 3.9 active drugs (median 2). The most common treatment indications identified in the study period were hypertension and depression, followed by pain and inflammation, and diabetes mellitus, respectively (tables I and II).

The sensitivity of the electronic prescribing system in documenting treatment indication was 98.5% (95% CI 96.5, 99.5) [figure 2]. For five drugs, the indications were entered manually and could not be interpreted. The PPV of the system in correctly identifying the treatment indication was 97.0% (95% CI 94.2, 98.6). Among the ten false positives, errors in selection (clicking a different indication than intended) is a probable cause in three cases since the correct indication was just above or below the incorrect indication but was not selected. Six of the incorrect indications shared pathophysiology or symptomatology with the correct indications obtained by the chart review; however, the chart-documented indications were not listed under the respective drug indication list. An example includes recording the indication 'pain' when the correct indication 'fibromyalgia' was not found in the list. This suggests that there is a tendency to select the conceptually closest indications when the correct one is not presented.

Table I. Characteristics of patients

Characteristics	Value
Age in years [mean (median)]	58.2 (60)
No. of active drugs [mean (median)]	3.9 (2)
No. of medical problems [mean (median)]	8.3 (9)
Female [n (%)]	210 (62.1)

Table II. Most frequently occurring treatment indications

Treatment indications	Frequency (%)
Hypertension	67 (19.8)
Depression	57 (16.9)
Pain and inflammation	40 (11.8)
Diabetes mellitus	32 (9.5)
Hypercholesterolaemia	25 (7.4)
Hypothyroidism	20 (5.9)
Gastroesophageal reflux	18 (5.3)
Osteoporosis	12 (3.6)
Hormone replacement	11 (3.3)

The sensitivity and PPV of the electronic prescribing system were 100% for hypertension, coronary heart disease, diabetes, hypercholesterolaemia, osteoporosis, hypothyroidism and gastroesophageal reflux. For depression, sensitivity was 100%, while PPV was 91.2%. Hormone replacement for menopause and andropause was documented with a sensitivity of 84.6% and a PPV of 100%. The system had 97.7% sensitivity and PPV for the indication pain and inflammation.

Of the 338 drugs, 28 (8.3%) were prescribed for off-label indications. The majority of these drugs were CNS agents (table III), including amitriptyline (indications: chronic pain and insomnia); gabapentin (indications: neurogenic and neuropathic pain) and clonazepam (indication: restless leg syndrome and anxiety). All drugs prescribed for hypertension, diabetes, hypercholesterolaemia, osteoporosis and hypothyroidism were approved for these indications.

		Chart review		
		Correct treatment indication	Incorrect treatment indication	Total
Electronic prescribing system	Indication documented	323	10	333
	Indication not documented	5	TN	TN + 5
	Total	328	TN + 10	338

Fig. 2. Sensitivity and positive predictive value (PPV) of the Medical Office for the XXI century (MOXXI) application in documenting treatment indications. Sensitivity (Completeness) = (TP)/(TP + FN) = 323/(323 + 5) = 98.5%; PPV (Correctness) = (TP)/(TP + FP) = 323/(323 + 10) = 97.0%, where **FN** = false negatives; **FP** = false positives; **TN** = true negatives; **TP** = true positives.

Table III. Study drugs and their off-label treatment indications

Drug	Off-label indications	No. of occurrences
Amitriptyline	Chronic pain	4
Gabapentin	Neurogenic (neuropathic) pain	4
Clonazepam	Restless leg syndrome	2
Amitriptyline	Insomnia	2
Citalopram	Obsessive-compulsive behaviour	2
Clonazepam	Anxiety	2
Atenolol	Anxiety	1
Paroxetine	Alcoholism	1
Risperidone	Alcoholism	1
Bupropion	Alcoholism	1
Desipramine	Attention-deficit syndrome	1
Amiodarone	Angina	1
Quetiapine	Depression	1
Citalopram	Generalized anxiety disorder	1
Hydroxyurea (hydroxycarbamide)	Essential thrombocytopenia	1
Nortriptyline	Migraine	1
Propranolol	Post-traumatic stress disorder	1
Tiotropium	Bronchial asthma	1
Total		**28**

Discussion

This is the first study to assess the accuracy of treatment indication recorded at the point of care in an electronic prescribing application and to determine the utility of indication captured in this manner for assessing on- and off-label prescribing. We found that treatment indication was recorded with high sensitivity (completeness) and PPV (correctness) using an electronic prescribing system. Moreover, it was demonstrated that the treatment indication data could be used to assess whether the drug was prescribed for approved indications or was being used off-label.

To our knowledge, no study has evaluated the accuracy of an electronic prescribing system in documenting treatment indication at the time of prescribing. However, studies have been conducted on the validation of recording health problems in electronic medical records. A validation study of 41 practices in the General Practice Research Database that compared diagnostic information extracted from computer records against paper charts and patient interview reported a sensitivity of 75% and PPV of 100%; it also reported a sensitivity and specificity of 100% for diabetes and depression.[15] A systematic review published in 2003 reported sensitivities of electronic health records ranging from 55% to 96% and PPV ranging from 96% to 100% in capturing health conditions.[17] Generally, the MOXXI electronic prescribing system performed better than these systems because of the fact that the documentation of treatment indication was standardized for a specific drug, plus it was a mandatory requirement. Moreover, documentation of the treatment indication provided a value-added benefit for the physician since this information is used to populate the patient's health problem list and all drugs are checked against the indication for possible drug-disease interaction. Entering an incorrect indication will also result in getting false drug-disease interaction alerts.

Our study shows that an electronic prescribing system that captures treatment indication can be used to assess the prevalence of off-label prescribing for all drug classes and medical conditions. Most off-label prescribing studies have

focused on a single diagnosis or narrowly defined areas such as HIV, psychiatry or children, and only a few studies have estimated the overall magnitude of off-label prescribing by employing a sentinel survey of physicians.[20,21] The treatment indication data can also be used to estimate prevalence of health problems, evaluate compliance to the standard of care, estimate compliance of drugs by indication, and to evaluate the safety and effectiveness of drugs for particular indications.

The study had a number of strengths. First, the administration of physician-facilitated chart reviews soon after patients' visits likely enhanced the accuracy of information about the treatment indication(s) for prescribed drugs. If chart review was done without the physician input, it would not have allowed us to link the drugs to the treatment indications since drugs and medical problems (or diagnoses) are written on the medical chart separately and linking would be even more difficult if the drug was prescribed for an off-label indication or for a previously undocumented indication. Second, blinding of the physicians and the interviewers to the treatment indication minimized possible observer and diagnosis review bias. Third, the distribution of treatment indications in this study is comparable with the distribution of treated health problems in Canada where the top eight indications in this study are among the ten top diagnoses treated with drugs.[22] Because of the lack of published standards on how to design and report data accuracy studies,[16] it was suggested that future studies should report numerical measures of both completeness and correctness, use unbiased sample selection to reflect the underlying population, select a gold standard that approximates the true state of the patient, and blinding of the reviewers when a gold standard is administered. We believe our study fulfills most of these requirements.

One reason the electronic system failed to correctly capture some treatment indications was the inability to identify and provide all off-label indications within the electronic system to physicians. While free-text entry is part of the application, the lack of standardization hampers the usability of the data. The creation of a searchable indications list from the treatment indications database should address this problem. To search for drugs, the MOXXI application uses 'autocompletion', where the first three letters entered retrieve a list of all drugs beginning with those letters. This is one of the features of the system identified by the physicians as being important in saving time.[9] In the future, the same strategy will be used for treatment indication to capture undocumented off-label indications. These efforts may further increase the PPV of electronic prescribing systems in capturing the correct treatment indications. The study also shows that even with a mandatory requirement for treatment indication documentation, some indications can be missed because of errors in interacting with the computer and an incomplete drug knowledge database.

Another limitation of the study is the exclusion of physicians with less than 2 years of experience in using the electronic prescribing system. Physicians with less experience in electronic prescribing may make more errors than established physicians. This would reduce sensitivity and PPV, at least in the short term as this technology is being adopted.

Governments and health systems are spending billions of dollars to implement electronic health records.[23,24] This investment presents a timely opportunity to identify critical elements of health data that can be used to evaluate the safety and effectiveness of drugs, including treatment indications and outcomes (e.g. discontinuation of a drug due to ADRs or ineffectiveness). Treatment indication can be documented at the time of prescribing. This information facilitates the evaluation and dispensing of drugs by the pharmacist and helps educate the patient about the reasons for taking the medication. Our study shows that physicians can document treatment indication with high accuracy at the time of prescribing using an electronic prescribing system. This process can be integrated into their workflow. Data from point-of-care systems can be analysed in real-time (based on a specified set of rules) and can be used to aid in decision making. The best illustration of this capacity is

the implementation of online adjudication systems for drug insurance plans that provide immediate feedback, at the point of purchase on coverage and patient co-pay requirements.[25] Our system has the capacity to collect, in real-time, reasons for discontinuation of drugs due to ADRs. This information can be made available, in real-time, to the prescribing physician as well as other physicians. Broad-scale adoption of electronic documentation of treatment indication nationally and internationally, coupled with information on drug discontinuations, would allow the creation of data in real-time to evaluate the safety and effectiveness of drugs in relation to the treatment indication.

Conclusions

The electronic prescribing system offers a valid method for documenting treatment indication at the time of prescribing. Our results provide strong evidence to support incorporating mandatory recording of treatment indication in integrated electronic prescribing systems to provide a critical piece of information for the evaluation of safety and effectiveness of drugs.

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HEALTH CARE REFORM

Drug, Patient, and Physician Characteristics Associated With Off-label Prescribing in Primary Care

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Background: Off-label prescribing may lead to adverse drug events. Little is known about its prevalence and determinants resulting from challenges in documenting treatment indication.

Methods: We used the Medical Office of the XXI Century electronic health record network in Quebec, Canada, where documentation of treatment indication is mandatory. One hundred thirteen primary care physicians wrote 253 347 electronic prescriptions for 50 823 patients from January 2005 through December 2009. Each drug indication was classified as on-label or off-label according to the Health Canada drug database. We identified off-label uses lacking strong scientific evidence. Alternating logistic regression was used to estimate the association between off-label use and drug, patient, and physician characteristics.

Results: The prevalence of off-label use was 11.0%; of the off-label prescriptions, 79.0% lacked strong scientific evidence. Off-label use was highest for central nervous system drugs (26.3%), including anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%). Drugs with 3 or 4 approved indications were associated with less off-label use compared with drugs with 1 or 2 approved indications (6.7% vs 15.7%; adjusted odds ratio [AOR], 0.44; 95% CI, 0.41-0.48). Drugs approved after 1995 were prescribed off-label less often than were drugs approved before 1981 (8.0% vs 17.0%; AOR, 0.46; 95% CI, 0.42-0.50). Patients with a Charlson Comorbidity Index of 1 or higher had lower off-label use than did patients with an index of 0 (9.6% vs 11.7%; AOR, 0.94; 95% CI, 0.91-0.97). Physicians with evidence-based orientation were less likely to prescribe off-label (AOR, 0.93; 95% CI, 0.88-0.99), a 7% reduction per 5 points in the evidence section of the Evidence-Practicality-Conformity Scale.

Conclusions: Off-label prescribing is common and varies by drug, patient, and physician characteristics. Electronic prescribing should document treatment indication to monitor off-label use.

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OFF-LABEL PRESCRIBING, the use of drugs for indications that have not received regulatory approval, is common, occurring with up to 21% of prescribed drugs.[1] Although the absence of regulatory approval for a treatment indication does not mean a drug is harmful in that circumstance, off-label use is suspected to be an important determinant of preventable adverse drug events. Indeed, off-label use of fenfluramine-phentermine was shown to cause cardiac valve damage.[2,3] When tiagabine, a drug approved to treat partial seizures, was used off-label to treat psychiatric conditions, seizures and status epilepticus occurred.[4] More recently, the use of quinine for nocturnal leg cramps, an off-label indication, resulted in serious adverse drug events, including thrombocytopenia and gastrointestinal bleeding.[5] However, there has not been any systematic investigation of the risks and benefits of off-label use beyond single drugs.[6]

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In addition, little is known about the factors that contribute to off-label prescribing that may determine systematic differences in treatment outcome. The paucity of knowledge is in part related to the methodologic challenges of measuring off-label use and its effects.[7] In most settings, treatment indication is not a required element of prescription. The indication for treatment needs to be inferred by reviewing either health problems documented in the patient's chart or diagnostic codes entered in physician surveys. For off-label use, the reason for treatment is, there-

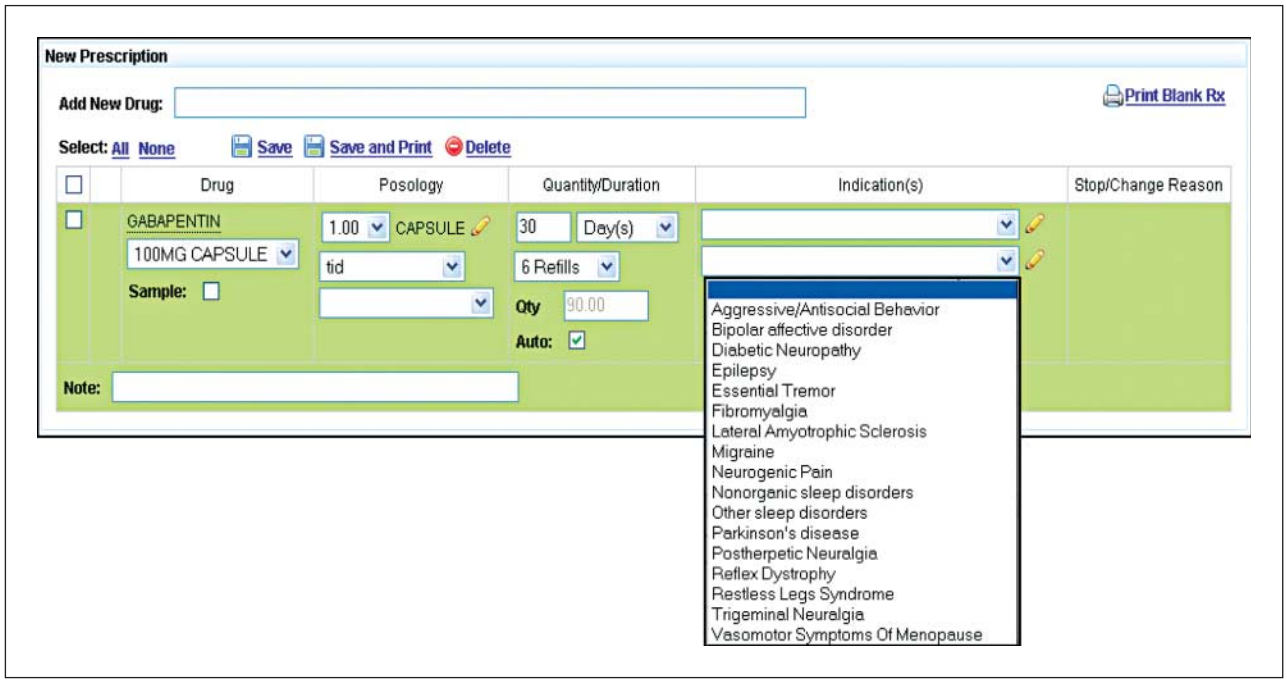

Figure 1. Documentation of treatment indication in the Medical Office of the XXI Century electronic prescribing system.

fore, difficult to discern.[1,8] Inclusion of treatment indications as a required field of an electronic prescription has been proposed as one method of addressing this problem and enhancing pharmacosurveillance.[7-10] To our knowledge, this study is the first to take advantage of the inclusion of treatment indication in an electronic health record (EHR) to evaluate off-label use and assess drug, patient, and physician factors that influence off-label prescribing.

METHODS

CONTEXT AND STUDY POPULATION

The Medical Office of the XXI Century (MOXXI) primary care EHR network research program was used as a source of data.[11] There are 113 primary care physicians and 50 823 patients in this research program. Eligible physicians practice in urban centers in Quebec, Canada; work in an office-based practice for 3 or more days per week; and are located within 40 km of the research offices. Overall, 410 physicians met these criteria, and 113 physicians (27.6%) consented to participate in this study. On average, participating physicians were 5 years younger than nonparticipating physicians. All patients who received electronic prescriptions from these physicians and all prescriptions written between January 1, 2005, and December 31, 2009, for drugs used by these patients were evaluated for this study. Ethics approval was granted by the McGill Faculty of Medicine Institutional Review Board.

Three features of the MOXXI EHR permit off-label use to be documented accurately. First, the system requires selection of a treatment indication for each electronic prescription from a menu of on-label and off-label indications (**Figure 1**). Second, therapeutic indications for a specific drug are updated monthly by a commercial vendor through review of drug monographs, compendiums, and published studies.[12] Third, unlisted off-label indications can be entered in a free-text field. To enhance the value for clinicians of recording treatment indication, 2 useful features are provided. First, documented treatment indications become part of the patient's problem list. Second, the history of drugs used with each treatment indication is recorded, including drug discontinuations and dosage changes, along with the reason for treatment failures (eg, hypotension).[13] As a result, the drug treatment indication data have been shown[14] to be highly accurate, with a positive predictive value of 97% and sensitivity of 98.5%.

OFF-LABEL USE

Each prescription was classified as on-label or off-label according to the Health Canada drug approval database.[15] Indications were considered to be Health Canada approved (ie, on-label) if they could be matched to the therapeutic indication reported in the drug's package insert as of December 2010, regardless of dosage, frequency, route of administration, duration of treatment, and patients' age range. Any indication that could not be matched to the labeled indication was considered off-label. For each off-label drug indication pair, the level of evidence supporting the drug's overall efficacy was categorized with the DrugPoints System, which uses the same drug information as DrugDex (both Thomson Reuters). These systems, which are used by Medicare/Medicaid to determine reimbursement for drugs,[16] describe the relationship between drug and treatment indication using 3 dimensions: level of efficacy (effective, favors efficacy, inconclusive, or ineffective), strength of recommendation (for all patients, most patients, specific patients, or not recommended), and strength of evidence (randomized controlled trial [RCT] with consistent results, RCT with inconsistent results, or no RCT). We followed a published algorithm[8] and used these dimensions to determine whether there is strong scientific evidence for the off-label use of a drug for a particular treatment indication. Strong evidence exists when (1) the drug is effective or favors efficacy for a particular treatment indication, (2) the drug is recommended for most or all patients with the treatment indication, and (3) the studies used to evaluate efficacy and the strength of evidence included at least 1 RCT.[8]

POTENTIAL RISK FACTORS FOR OFF-LABEL PRESCRIBING

Drug Characteristics

We measured *drug class* as a potential risk factor for off-label use because research[1] has shown that medications approved for psychiatric and allergy indications are more likely than other agents to be prescribed off-label. Drugs were classified using the American Hospital Formulary Service (AHFS). *Drug age*, defined as the year the drug was approved for marketing, was included because drugs that have been on the market longer have had a greater opportunity for off-label use. Drug age was categorized into 3 groups (before 1981, between 1981 and 1995, and after 1995). The *number of approved indications for a drug*, defined as a count of Health Canada–approved indications, was included because drugs with fewer approved indications may have a higher likelihood of being prescribed off-label.

Patient Characteristics

Age, sex, and comorbidity (Charlson Comorbidity Index) were assessed because older patients and those with a comorbidity may be less likely to receive off-label prescriptions owing to higher risks of adverse events.[17] Pharmacokinetic and pharmacodynamic factors differ between males and females,[18] resulting in varied responses to certain drugs,[19] which may increase the chance of receiving prescriptions for off-label drugs.[20]

Physician Characteristics

We measured 3 physician characteristics. Years since graduation from medical school was used as a proxy for physicians' knowledge of drugs. Older physicians are more likely to use drug detailers as a source of drug information and, therefore, may be more likely to prescribe off-label.[21,22] Physician sex was included because male physicians are more likely to prescribe new drugs than are female physicians.[23,24] We hypothesized that physicians who follow evidence-based medicine would be less likely to prescribe off-label. We used the evidence scale from the Evidence-Practicality-Conformity questionnaire.[25] This scale predicts clinical guideline compliance and measures the extent to which a physician prefers scientific evidence as the best source of knowledge in clinical decision making (eg, on-label prescribing) compared with clinical experience or opinion leaders.[25,26] High scores in the evidence scale indicate evidence-based orientation.

STATISTICAL ANALYSIS

The prevalence of off-label prescriptions was calculated by dividing the number of off-label prescriptions by the total number of prescriptions for a given drug, drug class, and overall. In addition, off-label use was partitioned into off-label with and without strong scientific evidence. The prevalence of off-label use without strong scientific evidence was calculated using off-label prescriptions as a denominator.

To assess determinants of off-label use, a multilevel approach was used, with prescription (drug-indication pair) being the unit of analysis. Drug, patient, and physician characteristics represented the 3 levels in the analysis, and clustering of drugs within each patient and patients within each physician was accounted for using alternating logistic regression, a multilevel analytic approach for binary outcomes.[27-29] In alternating logistic regression, within-patient and within-physician clustering is described with pairwise odds ratios (ORs) rather than intraclass correlations. Two outcome variables were evaluated: off-label status (yes/no) and off-label status without strong evidence vs on-label and off-label status with strong evidence.

RESULTS

A total of 650 237 electronic prescriptions were written between January 2005 and December 2009 and a total of 253 347 unique patient and drug indication combinations were identified once repeated prescriptions were removed, representing 50 823 patients, 113 physicians, and 684 drugs. Overall, 11.0% of drugs were prescribed for an off-label indication and 79.0% of off-label use lacked strong scientific evidence (**Table 1**).

Variation in off-label prescribing was observed among drug classes (Table 1). The highest proportion of off-label prescribing occurred with central nervous system drugs (26.3%), anti-infective agents (17.1%), and ear-nose-throat medications (15.2%). Among central nervous system drugs, the highest proportions of off-label use were for anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%) (**Figure 2**). The lowest off-label prescribing was for formulary-restricted drugs (2.9%) and blood and coagulation drugs (1.7%). Scientific support for an off-label use was lowest for antineoplastic (0%) and ear-nose-throat (1.6%) drug classes and highest for cardiovascular (58.8%) and dermatologic (65.9%) drug classes.

Specific drugs with the highest off-label use included quinine sulfate (99.5% of prescriptions) followed by gabapentin (99.2%), clonazepam (96.2%), amitriptyline hydrochloride (93.7%), trazodone hydrochloride (92.6%), and betahistine dihydrochloride (91.5%) (**Table 2**). Among the top 15 drugs with the highest off-label use, 8 did not meet study criteria for having strong scientific evidence. The lowest prevalence of off-label use was for antidiabetics (0%-2%), lipid-lowering agents (0%-0.5%), and antimigraine medications (0%).

Indications that were most likely to be treated with off-label drugs included nocturnal leg pain and benign positional vertigo, for which 100% of the drugs prescribed were off-label (**Table 3**). Neurogenic pain was treated off-label 99.5% of the time with drugs, including gabapentin, amitriptyline, and topiramate. Other indications with high rates of off-label prescribing included fibromyalgia (67.0%), arrhythmia (60.2%), generalized anxiety disorder (46.5%), and insomnia (43.6%).

Absolute rates of off-label use and off-label use without strong evidence stratified by drug, patient, and physician characteristics are reported in **Table 4**. Older drugs (approved before 1996), drugs with 1 or 2 approved indications, and the oldest and the sickest patient groups had more scientifically supported off-label use compared with their counterparts. Pairwise ORs for within-patient and within-physician clustering with no covariates were 1.24 (95% CI, 1.21-1.29) and 1.07 (95% CI, 1.04-1.09), respectively, indicating that off-label clustering was greater within patient than within physician.

Table 1. Distribution of Off-label Use by AHFS Therapeutic Class and the Level of Scientific Support

Drug AHFS Class	No. of Prescriptions	Off-label Use, No. (%)	Proportion of Off-label Use by Degree of Scientific Evidence, %[a,b]	
			With Strong Evidence	Without Strong Evidence
Central nervous system	58 914	15 491 (26.3)	18.2	81.8
Ear-nose-throat	10 622	1613 (15.2)	1.6	98.4
Gastrointestinal	14 237	1770 (12.4)	15.1	84.9
Hormone and synthetics	34 868	1366 (3.9)	34.5	65.5
Skin and mucous membrane	15 815	760 (4.8)	65.9	34.1
Formulary restricted	11 174	327 (2.9)	48.6	51.4
Antihistamine	348	21 (6.0)	19.0	81.0
Anti-infective	21 000	3599 (17.1)	4.6	95.4
Antineoplastic	234	28 (12.0)	0	100.0
Autonomic	13 854	540 (3.9)	12.2	87.8
Blood and coagulation	1328	23 (1.7)	0	100.0
Cardiovascular	70 953	2313 (3.3)	58.8	41.2
Total	**253 347**	**27 851** (11.0)	21.0	79.0

Abbreviation: AHFS, American Hospital Formulary Service.

[a] The proportion of off-label use according to scientific evidence was calculated using the number of off-label prescriptions as a denominator. For example, 18.2% of the 15 491 off-label central nervous system prescriptions had strong scientific evidence for their use. Of the 27 851 total off-label prescriptions, 21.0% had strong scientific evidence.

[b] DrugPoints synthesizes efficacy data, strength of evidence, and the level of recommendation to categorize degree of existing scientific evidence for each drug indication (off-label) pair. A published algorithm[8] was used to categorize whether strong scientific evidence exists according to the DrugPoints classification.

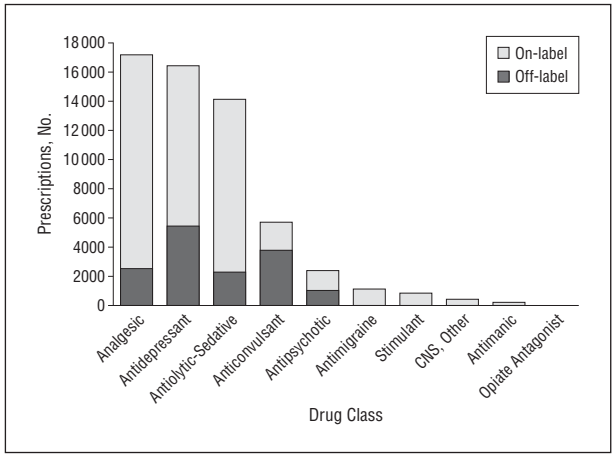

Figure 2. Frequency distribution of central nervous system (CNS) drugs by drug approval status (on-label and off-label).

In a multivariable analysis, central nervous system drugs were associated with more off-label use than were cardiovascular drugs (26.3% vs 3.3%; adjusted OR [AOR], 9.91; 95% CI, 9.07-10.84), and formulary-restricted drugs had lower off-label use (2.9%; AOR, 1.01; 95% CI, 0.87-1.16). Drugs with 3 or 4 approved indications had lower off-label use compared with drugs with 1 or 2 approved indications (6.7% vs 15.7%; AOR, 0.44; 95% CI, 0.41-0.48). In addition, drugs with 5 to 7 and those with 8 or more approved indications had lower off-label use: 9.6% (AOR, 0.62; 95% CI, 0.57-0.67) and 9.7% (AOR, 0.32; 95% CI, 0.28-0.37), respectively. Drugs approved after 1995 had lower off-label use than did drugs approved before 1981 (8.0% vs 17.0%; AOR, 0.46; 95% CI, 0.42-0.50); drugs approved between 1981 and 1995 also had lower off-label use than those approved before 1981 (8.4%; AOR, 0.48; 95% CI, 0.43-0.55). Women received more off-label drugs compared with men (11.8% vs 9.7%; AOR, 1.06; 95% CI, 1.03-1.09). Patients with a Charlson Comorbidity Index score of 1 or higher had lower off-label use than did those with a Charlson Comorbidity Index score of 0 (9.6% vs 11.7%; AOR, 0.94; 95% CI, 0.91-0.97). Physicians with higher scores on evidence-based practice were less likely to prescribe off-label. A 5-point increase in the physicians' evidence score on the Evidence-Practicality-Conformity Scale decreased the risk of off-label prescribing by 7% (AOR, 0.93; 95% CI, 0.88-0.99). Patient age, physician sex, and physician graduation year were not associated with off-label use. When the analysis was restricted to off-label prescribing without strong evidence, there were notable differences (Table 4). The AOR for the central nervous system, anti-infective, ear-nose-throat, and antineoplastic drug classes increased by more than 2-fold owing to small percentages of off-label use with strong scientific support in these classes and a large percentage of strong scientific support in the cardiovascular (reference) group. Older drugs and drugs with 1 or 2 approved treatment indications still had the highest risk for off-label use; however, the risk was attenuated. Physicians who graduated in the 1980s and those who graduated in the 1990s-2000s prescribed off-label without scientific evidence more frequently than did the 1960-1970 graduates. In addition, the physician evidence-based practice score had a stronger effect on off-label prescribing without scientific evidence, with a 5-point increase in physicians' evidence scale decreasing off-label prescribing without scientific evidence by 10% (AOR, 0.90; 95% CI, 0.85-0.96).

COMMENT

To our knowledge, this is the first study to assess off-label prescribing using an EHR platform that explicitly linked treatment indications to prescribed drugs. By using novel, validated drug indication data collected at the time of prescribing, we were able to address the 2

Table 2. Off-label Use by Drug and the Degree of Scientific Evidence

Drug Name	No. of Prescriptions	%		
		Off-label	With Strong Evidence[a]	Without Strong Evidence[a]
Quinine sulfate	953	99.5	0	100.0
Gabapentin	840	99.2	4.0	96.0
Clonazepam	2370	96.2	1.1	98.9
Amitriptyline hydrochloride	1670	93.7	45.4	54.6
Trazodone hydrochloride	1700	92.6	0	100.0
Betahistine dihydrochloride	715	91.5	0	100.0
Oxazepam	2132	72.0	98.1	1.9
Quetiapine fumarate	983	66.7	0	100.0
Azithromycin	2155	65.7	3.7	96.3
Olanzapine	478	54.2	0	100.0
Diclofenac sodium + misoprostol	899	53.1	18.2	81.8
Risperidone	480	43.8	0	100.0
Celecoxib	3987	42.4	0	100.0
Bisoprolol fumarate	1661	40.4	97.9	2.1
Citalopram hydrobromide	2973	35.6	0	100.0

[a] The 2 percentages total 100%. For example, only 4.0% of the 99.2% of gabapentin off-label use had strong scientific evidence; the rest (96.0%) had no strong scientific evidence.

Table 3. Top 10 Clinical Indications Treated With Off-label Drugs and Their Most Frequent Off-label Drugs[a]

Treatment Indication	No. of Prescriptions	Off-label, No. (%)	Drug Name, %		
			Most Common Off-label Drug	Second Most Common Off-label Drug	Third Most Common Off-label Drug
Benign positional vertigo[b]	653	653 (100.0)	Betahistine (100.0)	. . .	. . .
Nocturnal leg pain[b]	948	948 (100.0)	Quinine (100.0)	. . .	. . .
Neurogenic pain	1153	1147 (99.5)	Gabapentin (51.5)	Amitriptyline (15.5)	Topiramate (7.8)
Chronic pain	251	213 (84.9)	Amitriptyline (90.1)	Gabapentin (0.9)	Nabilone (0.5)
Fibromyalgia	816	547 (67.0)	Cyclobenzaprine (74.0)	Gabapentin (11.0)	Venlafaxine (6.0)
Arrhythmia	752	453 (60.2)	Metoprolol (37.1)	Atenolol (34.3)	Nadolol (18.7)
Generalized anxiety disorder	3275	1522 (46.5)	Citalopram (54.7)	Clonazepam (13.7)	Sertraline (12.6)
Insomnia	10 392	4535 (43.6)	Oxazepam (33.2)	Trazodone (29.9)	Clonazepam (11.7)
Bipolar disorder	643	177 (27.5)	Lamotrigine (74.0)	Topiramate (13.6)	Gabapentin (11.3)
Diabetic neuropathy	338	68 (20.1)	Gabapentin (89.7)	Pentoxifylline (5.9)	Paroxetine (4.4)

[a] The drugs, treatment indications, and off-label status are based on the Health Canada drug database.[15] Some drugs included in this table may not be approved in other countries. Some off-label indications may be listed as an approved indication in other countries. For example, gabapentin was approved for only 1 indication (adjuvant therapy for partial seizures) in Canada and the United States; postherpetic neuralgia was added to the labeled indications in 2004 in the United States.

[b] Treatment indications with no approved drugs.

most important drawbacks in the assessment of off-label prescribing: lack of a link between the prescribed drug and its indication for use and the drug, patient, and physician characteristics associated with off-label prescribing. Moreover, it was possible to identify treatment indications associated with a high prevalence of off-label drug use that would benefit from new drug development or RCTs.

In this study, we found that 11% of drugs were prescribed off-label and that, among these, 79% lacked strong scientific evidence. The magnitude of off-label use was less than in a US study.[1] The difference in off-label use can be explained by the difference in the drugs and populations examined. Our study included all drugs prescribed to an adult population (predominantly older); the US study included 160 drugs prescribed for adults and children. However, the proportion of off-label use not supported by strong scientific evidence was comparable. Both studies found that psychiatric and anticonvulsant drugs had the highest off-label use. In our study, formulary-restricted drugs had lower off-label use, probably because physicians had to justify the use of the drug for the specific indication or had to try other drugs first, which is known to affect prescribing.[30] A physician's lack of knowledge about drugs[31] and the scarcity of approved or efficacious drugs may be reasons for some of the off-label prescribing.[32,33]

The reasons for the association of older drugs with off-label use include that these medications have been on the market longer, thereby creating the opportunity for experimentation and discovery of new uses by clinicians.[34] In addition, these drugs are off-patent, with no sponsor to perform RCTs or apply for the inclusion of new indications to the label.[35] Contrary to a previous study,[1] we observed that drugs with fewer approved indications had higher rates of off-label use. However, some single-indication drugs, such as antimigraine and antidiabetic agents, had the lowest level of off-label prescrib-

Table 4. Proportion of Off-label Prescribing and Multivariate Analysis With 2 Outcomes: Off-label and Off-label Without Strong Scientific Evidence

Variable	Off-label, %	AOR (95% CI)	Off-label Without Strong Scientific Evidence, %	AOR (95% CI)
Drug age				
Before 1981	17.0	1 [Reference]	13.0	1 [Reference]
1981-1995	8.4	0.48 (0.43-0.55)	6.0	0.45 (0.39-0.52)
1996-2009	8.0	0.46 (0.42-0.50)	7.4	0.67 (0.61-0.73)
Drug class				
Cardiovascular	3.3	1 [Reference]	1.3	1 [Reference]
CNS	26.3	9.91 (9.07-10.84)	21.6	19.42 (17.38-21.69)
Anti-infective	17.1	9.53 (8.09-11.23)	16.6	22.54 (18.82-26.99)
ENT	15.2	5.23 (4.63-5.91)	15.1	14.10 (12.14-16.38)
Gastrointestinal	12.4	8.77 (7.22-10.66)	10.6	14.97 (12.02-18.65)
Antineoplastic	12.0	3.29 (2.17-5.00)	11.9	9.50 (6.21-14.54)
Antihistamine	6.0	0.75 (0.43-1.29)	4.9	1.97 (1.06-3.66)
Skin and mucous membrane	4.8	1.57 (1.37-1.79)	1.7	1.32 (1.06-1.65)
Hormone and synthetics	3.9	1.21 (1.05-1.39)	2.6	2.00 (1.71-2.34)
Autonomic	3.9	1.11 (0.94-1.31)	3.6	2.50 (2.10-2.98)
Formulary restricted	2.9	1.01 (0.87-1.16)	1.5	1.15 (0.94-1.42)
Blood and coagulation	1.7	0.65 (0.41-1.01)	1.7	1.64 (1.05-2.55)
Approved indication count				
1-2	15.7	1 [Reference]	11.2	1 [Reference]
3-4	6.7	0.44 (0.41-0.48)	5.7	0.62 (0.57-0.68)
5-7	9.6	0.62 (0.57-0.67)	7.8	0.83 (0.76-0.91)
>8	9.7	0.32 (0.28-0.37)	8.7	0.44 (0.37-0.51)
Patient age, y				
<48.5	13.6	1 [Reference]	11.5	1 [Reference]
48.6-60.5	12.4	1.04 (1.00-1.09)	10.2	1.03 (0.98-1.08)
60.6-71.5	10.3	1.04 (0.98-1.09)	8.1	1.02 (0.96-1.08)
>71.5	9.2	1.01 (0.96-1.07)	6.8	0.95 (0.90-1.01)
Patient sex				
Male	9.7	1 [Reference]	7.6	1 [Reference]
Female	11.8	1.06 (1.03-1.09)	9.4	1.05 (1.02-1.09)
Charlson Comorbidity Index				
0	11.7	1 [Reference]	9.4	1 [Reference]
≥1	9.6	0.94 (0.91-0.97)	7.4	0.95 (0.92-0.99)
Physician graduation year				
1960-1979	10.6	1 [Reference]	8.3	1 [Reference]
1980-1989	11.2	1.08 (1.00-1.16)	9.0	1.10 (1.01-1.19)
1990-2004	11.3	1.08 (0.99-1.18)	9.1	1.11 (1.01-1.21)
Physician sex				
Male	11.2	1 [Reference]	8.9	1 [Reference]
Female	10.7	0.99 (0.93-1.05)	8.5	0.98 (0.92-1.05)
Physician evidence scale, mean (SD) [range][a]	21.2 (2.5) [14-28]	0.93 (0.88-0.99)		0.90 (0.85-0.96)

Abbreviations: AOR, adjusted odds ratio; CNS, central nervous system; ENT, ear-nose-throat.

[a] Indicates the physician's attitude toward evidence-based medicine. The AOR is per 5-unit increase in the evidence scale in the Evidence-Practicality-Conformity instrument, which is a psychometric instrument developed by the University of Michigan[25] to study determinants of the adoption of evidence-based practice. The objective of the instrument is to capture physicians' variability in (1) judging the credibility of a source of information (evidence), (2) the emphasis given to practical concerns (practicality), and (3) the readiness to differ from the group norm in practice (conformity). The instrument underwent the various validation stages using more than 1200 physicians. The internal consistencies, measured by Cronbach α, were 0.79 for the evidence scale, 0.74 for the conformity scale, and 0.68 for the practicality scale. Physician characteristics measured by the instrument affect responses to clinical guideline implementation strategies.[26]

ing,[1] implying that their use is too specific to treat any other condition.

Sicker patients were less likely to receive off-label drugs, which may be the result of their poor health creating less room to "experiment" with a drug. This trend has also been observed in children.[36] In our study, women received more off-label prescriptions than men because women were more likely to be treated for problems such as anxiety, nocturnal leg pain, and insomnia, conditions for which off-label prescribing is common.

Physicians with evidence-based orientation were less likely to prescribe off-label, and this effect was increased for drugs prescribed off-label without strong scientific evidence. This observation implies that physicians who give emphasis to evidence-based medicine base their treatment decisions not only on data from drug regulatory bodies but also using the overall evidence available in sources, including peer-reviewed publications, clinical guidelines, and recommendations from professional societies. Currently, there is an effort to educate physicians on the level of evidence and appropriate off-label uses[37-39] with the aim of linking off-label use with rigorous outcome evaluation, with the physician being an active participant in evidence development. Connecting drugs with their treatment indications and providing evidence to support off-label use at the time of pre-

scribing would be one way of addressing scientifically unsupported off-label use.

This study has several limitations. First, the definition of *off-label* was conservative, since it did not include dosage, frequency, route of administration, duration of treatment, and patients' age range, which, if considered, would increase the prevalence of off-label prescribing. Second, some off-label use may be explained by comorbidities; however, the potential for misclassification was low owing to the explicit linking of drugs with their indications. Third, the compendium used to evaluate level of evidence for off-label use has limitations. The methods used to classify evidence are not transparent and the evidence is not necessarily up-to-date; however, this compendium documents a comprehensive list of off-label indications with their level of evidence better than other compendia.[8,16] Fourth, the physicians in the study were younger and were willing to use an EHR; this may limit the generalizability of the findings to other physician groups. Fifth, because we did not capture nonpharmacologic treatments and their indications, the findings are conditional on having a drug prescribed for an indication. We also could not directly compare the off-label rates using an EHR and previous methods because of the unavailability of nationally representative physician survey data in Canada.

Countries are spending billions of dollars to implement EHRs.[40,41] In the United States, objectives for "meaningful use" of EHRs were defined to achieve improvement in health care quality.[42] Maintaining an active medication and problem (diagnosis) list were among the core objectives identified that are essential to create a medical record. These 2 tasks are seamlessly integrated in the MOXXI electronic prescribing system, which generates the medication and problem lists in real time. Linking a prescribed drug with an indication could be a meaningful use objective, and vendors could easily incorporate this feature into EHR systems. Moreover, reasons for discontinuation of drugs (eg, adverse drug events and ineffective treatments) can be linked to treatment indications, creating a novel pharmacosurveillance tool to evaluate the safety and effectiveness of drugs,[13] thereby advancing meaningful use to meaningful benefit.[43] In addition, drug regulatory bodies may use the data (indication and reason for discontinuation) to facilitate the postmarketing surveillance of both on-label and off-label use of drugs at the time they enter the market.

In conclusion, our findings indicate that off-label prescribing is common in primary care and varies by drug class, the number of approved indications for the drug, the age of the drug, patients' sex, and physicians' attitude toward evidence-based medicine. Electronic health records can be used to document treatment indication at the time of prescribing and may pave the way for enhanced postmarketing evaluation of drugs if linked to treatment outcomes.

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Author Contributions: Drs Eguale and Tamblyn had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Eguale, Buckeridge, Winslade, and Tamblyn. *Acquisition of data*: Eguale and Tamblyn. *Analysis and interpretation of data*: Eguale, Buckeridge, Winslade, Benedetti, Hanley, and Tamblyn. *Drafting of the manuscript*: Eguale and Tamblyn. *Critical revision of the manuscript for important intellectual content*: Eguale, Buckeridge, Winslade, Benedetti, Hanley, and Tamblyn. *Statistical analysis*: Eguale, Benedetti, Hanley, and Tamblyn. *Obtained funding*: Tamblyn. *Administrative, technical, or material support*: Winslade and Tamblyn. *Study supervision*: Buckeridge and Tamblyn.
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Appendix C: Selected copies of media coverage of published article # 3

The Gazette
montrealgazette.com

Off-label drug use widespread: study

BY CHARLIE FIDELMAN, GAZETTE HEALTH REPORTER APRIL 17, 2012

In Quebec, a McGill University study says, 11 per cent of drug prescriptions are for uses not approved by Health Canada — and the majority of these off-label uses — up to 80 per cent — lack studies or scientific evidence for efficacy and safety.

Photograph by: Joe Raedle , Getty Images

MONTREAL - When your doctor prescribes an anti-malaria drug for painful leg cramps or anti-depressants for insomnia, you might assume the drugs have been approved for that use.

But a Quebec study has found that “off-label” drug use — that is, prescribing medications for conditions other than what the drug has been designed and approved to treat — is widespread.

In Quebec, the McGill University study says, 11 per cent of drug prescriptions are for uses not approved by Health Canada — and the majority of these off-label uses — up to 80 per cent — lack studies or scientific evidence for efficacy and safety.

A previous study in the United States found that one in five prescriptions in that country are not approved by the FDA.

While the U.S. study relied on physician surveys for 160 drugs, the Quebec study, run by a McGill University research team, captured hard data on 648 drugs prescribed to adults by looking at computerized records.

“We had every drug prescribed by family physicians to patients age 18 and older,” said lead author Tewodros Eguale, whose study evaluated off-label drug practices in Quebec based on electronic health records for 50,823 patients from January 2005 through December 2009 and involving 113 family doctors.

It’s already known that off-label drug use can have serious consequences for children, said Eguale, a researcher at McGill’s department of epidemiology, biostatistics and occupational health.

Monitoring off-label use is crucial to reducing adverse events. One the best known off-label incidents occurred in the ’90s when fen-phen – the unapproved combination of fenfluramine and phentermine as an obesity treatment – was banned after it was linked to heart damage.

But it’s hard to get good information on the scope of the problem because of “challenges in documenting treatment indication,” Eguale explained.

For example, anti-depressant use continues to rise, but it would be a mistake to assume that each prescription is for depression; 33 per cent were handed out for pain, insomnia and other complaints, the study showed.

The team needed a database where drug indication is a mandatory part of documentation. They turned to the Medical Office of the XXI Century, an electronic health record network in Quebec established as a McGill University research project to study the effects of computerized care.

“Now we can link this to a (drug) outcome,” Eguale said.

Not every Quebec physician is currently using e-records, but the McGill study, published online Monday in the Archives of Internal Medicine, confirms that off-label use is common, costly and can have negative consequences for the patient.

There were 71 adverse reactions recorded for quinine, an anti-malaria drug, but in only four cases was it prescribed for malaria, according to Health Canada, the researcher said.

The highest proportion of off-label prescribing involved drugs that act on the central nervous system, 26.3 per cent, and antibiotics and other anti-infection agents, 17.1 per cent. Also, 66 per cent of anticonvulsants, 44 per cent of antipsychotics and 33 per cent of antidepressants were prescribed for off-label conditions.

The biggest surprise revealed by the study is that up to 80 per cent of off-label prescriptions were not backed by strong scientific evidence.

Doctors who are informed by peer-reviewed, clinical studies tend to to prescribe off-label less often, but some simply didn't know they were giving their patients drugs that did not have Health Canada approval for certain conditions.

Older drugs that had been on the market longer were more likely to be used off-label than newer drugs.

The McGill study did not address the issue of physician education, but pharmaceutical companies spend billions marketing such drugs in education seminars.

"In the past eight years, pharmaceutical companies were fined more than $10 billion for illegal off-label promotion in the U.S.A.," Eguale noted. Last week, a U.S. court fined pharmaceutical company Johnson & Johnson $1.2 billion for misleading doctors about the risks associated with a best-selling anti-psychotic drug Risperdal.

The Canadian Medical Association has no policy on off-label drug use by physicians. Doctors are expected to follow a policy of "optimal prescribing" by prescribing a drug that is "most clinically appropriate for the patient's condition."

The study was funded by a grant from the Canadian Institutes of Health Research.

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Étude - Des médicaments prescrits en dehors de leur spectre d'action officiellement reconnu

Amélie Daoust-Boisvert 17 avril 2012 Santé

Photo : Agence Reuters Lucy Nicholson

La quinine, le gabapentin, le clonazepam, l'amitriptyline et le trazodone sont les médicaments les plus souvent prescrits off label.

La prescription de médicaments pour des indications non approuvées par Santé Canada est commune, selon des chercheurs de l'Unviersité McGill qui signent une étude dans Archives of Internal Medicine. Douleurs nocturnes aux jambes, vertige positionnel bénin, douleurs neuropathiques, fibromyalgie, arythmie et trouble de l'anxiété généralisé sont les maladies pour lesquelles les médecins se tournent le plus vers des médicaments dont l'efficacité n'a pas été sanctionnée.

Les chercheurs ont calculé que 11 % des médicaments sont prescrits en dehors de leur spectre d'action reconnu officiellement — ou off label, comme on dit en anglais. Ce taux est de moitié moins important que celui ayant cours chez nos voisins du Sud, selon une étude américaine. Parmi ces prescriptions, 79 % ne s'appuient pas sur des données scientifiques solides, selon l'étude signée par le Dr Tewodros Eguale et ses collègues.

La quinine, le gabapentin, le clonazepam, l'amitriptyline et le trazodone sont les médicaments les plus souvent prescrits off label.

Cette pratique peut entraîner des effets secondaires indésirables. Par exemple, la prescription d'une combinaison de fenfluramine et de phentermine à des patients obèses, sans sanction des autorités de santé, a causé des dommages cardiaques chez certains d'entre eux.

Les molécules utilisées depuis longtemps, comme la quinine, sont plus susceptibles d'être prescrites off label, remarquent les chercheurs, le temps ayant permis de leur découvrir de nouvelles utilités.

Mais une fois le brevet échu, les compagnies pharmaceutiques prennent moins souvent la peine de soumettre une demande auprès de Santé Canada pour faire approuver cette nouvelle indication. Selon les chercheurs, le manque de connaissance des médecins sur les médicaments ou l'absence de médicaments approuvés pour traiter certaines maladies seraient d'autres causes à explorer.

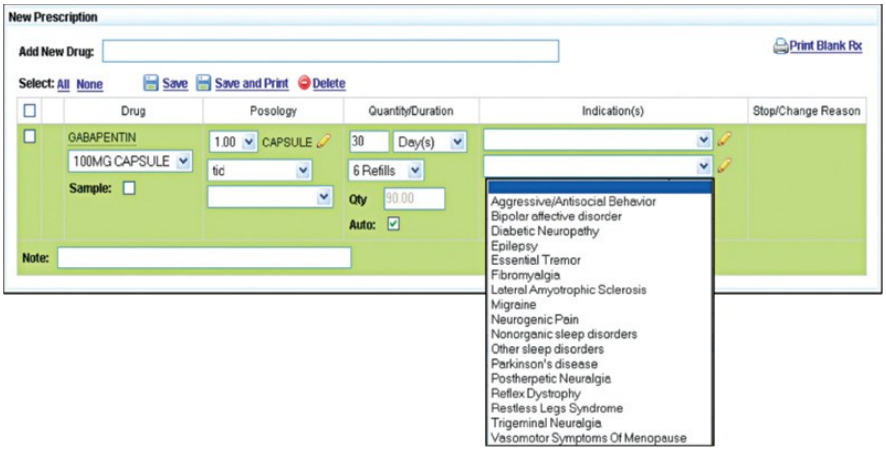
Les chercheurs ont analysé 253 347 prescriptions de 113 médecins participant à un projet de recherche qui les amène à utiliser un logiciel de prescription. Des études plus exhaustives sont nécessaires pour évaluer le phénomène à l'échelle du Québec.

FEATURES

Can IT Stop the Off-label Prescription Hemmorhage?

Written by Justine Cadet

June 25, 2012



Documentation of treatment indication in the Medical Office of the XXI Century (MOXXI) electronic prescribing system.

Source: Arch Intern Med 2012;172(10):781-788.

Off-label prescribing, the use of drugs for indications that have not received regulatory approval, occurs with up to 21 percent of prescribed drugs among office-based physicians (Arch Intern Med 2006;166(9):1021-1026). Yet, the problem isn't unique to the ambulatory setting. While individual providers are investigating the problem internally, comprehensive inpatient data aren't available. Off-label usage of prescription drugs is not illegal, but it has the potential to lead to wasteful or even harmful care in some instances, yet can be advantageous in others. Regardless, most experts agree in the value of tracking and properly assessing this practice.

Many administrators and physicians are starting to recognize the value of various health IT systems, such as EHRs, e-prescribing, computerized physician order entry (CPOE) and clinical decision support (CDS) as a means to track, collate data on and potentially, prevent widespread use of the more harmful practices.

First is data collection. Evaluating the MOXXI primary care EHR network in Canada between January 2005 and December 2009, Tewodros Eguale, MD, MSc, of McGill University in Montreal, et al found that 113 primary care physicians wrote 253,347 e-prescriptions for 50,823 patients. They classified each drug indication as on-label or off-label based on the Health Canada drug database, and identified off-label uses lacking "strong" scientific evidence (Arch Intern Med 2012;172(10):781-788).

"Our overall objective was to see how computerization helps the day-to-day activities of primary care physicians by giving them drug information and patient information," Eguale says. "Instead of relying on somewhat unreliable survey data, we implemented a treatment indication chapter within the EHR system, enabling us to capture very fine details of treatment indications."

In the study, the prevalence of off-label use was 11 percent, with 79 percent of the off-label prescriptions lacking strong scientific evidence. Off-label usage was highest for central nervous system

drugs (26.3 percent), including anticonvulsants (66.6 percent), antipsychotics (43.8 percent) and antidepressants (33.4 percent). Sicker patients were less likely to receive off-label drugs, which "may be the result of their poor health creating less room to 'experiment' with a drug." This trend also has been observed in children.

The bigger question may lie in understanding why and how physicians make their clinical decisions. "Traditionally, when physicians have written prescriptions, they do not have to write down an indication," explains Surrey Walton, PhD, of the University of Illinois at Chicago. "Indications are typically coded for billing purposes with ICD-9 codes tending to be broad, and therefore, they aren't very helpful for assessing clinical diagnostics or when trying to ascertain why a physician used one drug over another."

For improved prescribing, Eguale says that physicians need to be made aware of three things at the time of decision-making: whether the drug is approved; whether there is strong evidence to use a particular drug for a particular indication; whether there is any report of adverse drug reactions and the severity of that reaction.

The solution may be as simple as color coding on-label and off-label status in the CDS, or another technological or visual method of informing the physician of a potential error, suggests Eguale.

"Linking a prescribed drug with an indication could be a meaningful use objective, and vendors could easily incorporate this feature into EHR systems," the study authors wrote. "EHRs can be used to document treatment indication at the time of prescribing."

Inpatient introspection

Recognizing that off-label use might not be unique to the outpatient environment, a team at the University of Illinois at Chicago launched a pilot project to develop an electronic-based intervention for gathering data regarding off-label drug use in the inpatient setting. The project is seeking to identify and focus on specific drugs in an inpatient setting where there are particular clinical and economic concerns regarding off-label use. Also, the researchers are collecting data on the accuracy of physicians' answers when prompted about why they prescribed a particular medication.

Their single-center, inpatient study assessed a CDS system that was designed to obtain indications and document during CPOE ordering of drugs, which are frequently used off-label, namely the proton pump inhibitor (PPI), lansoprazole, the IVIG Flebogamma and the Factor VIIa Novoseven (Appl Clin Inf 2011;2:94-103).

More specifically, the study examined "what would happen if an IT system required physicians to explain more explicitly why they used certain drugs, and if they took a little longer to question their own reflex of prescribing a particular drug," says Randall S. Stafford, MD, PhD, of the Stanford University School of Medicine in Stanford, Calif. He adds that the factor VIIa use is particularly "concerning." The drug is indicated for bleeding episodes in hemophilia A or B patients, but is diffused into widespread use for a number of other leading situations, says Stafford. It also is very expensive at $40,000 to $50,000 for every use.

The PPI intervention generated 873 alerts during 60 days of operation; IVIG 55 alerts during 93 days; and Factor VIIa 25 alerts during 175 days. Agreement between indications entered and chart review was 63 percent for PPI, 49 percent for IVIG and 29 percent for Factor VIIa. The alerts for PPI, IVIG and

Factor VIIa produced accurate diagnoses for the problem list 9 percent of the time, 16 percent and 24 percent, respectively.

"This study illustrates substantial off-label use for certain medications and many challenges for obtaining indication information. In particular, the indication data generated in this pilot study were not highly accurate," Walton et al wrote. Yet, because the Joint Commission requires connection between indications for inpatient medication use and indications approved by a Pharmacy and Therapeutics Committee, "this type of CDS may help institutions comply" with these regulations. The authors added that prompts during CPOE to remind clinicians of a medication's indications may improve evidence-based use of medications and can improve problem list documentation.

Data collection is critical

The consensus on the need for improved data in this area might be best summarized by a recent editorial by Stafford. "Objective, comprehensive and comparative syntheses of data relating to off-label use of drugs would be valuable to prescribers, patients and healthcare payors," he wrote (Nature 2012;91(5)920-925). "Data from EHRs relating to drug prescriptions could provide an early alert if off-label use of a particular drug is increasing. In addition, data mining of claims data from multiple healthcare payors could help identify potential safety issues associated with off-label use."

Stafford says that the primary goal in attaining these metrics is to ensure patient safety by reducing the risk that somebody has an adverse effect of a medication, to improve cost-efficiencies by using cheaper drugs "if those drugs do pretty much the same thing as a more expensive drug."

As with many quality improvement initiatives, progress may come on a case-by-case basis. For instance, Eguale says that their MOXXI EHR system is tracking drug indications during treatment, as well as what happens with treatment down the line. Therefore, if a physician stops administering or change dose a particular medication, the EHR system has a mandatory requirement to input a reason (e.g. adverse drug reaction, ineffectiveness)—a novel method of generating data for CDS and pharmacosurveillance.

"With the treatment indication and treatment discontinuation features of the EHR, we have created a longitudinal record of 'drug-treatment indication-reason for drug discontinuation.'" Eguale says. Also, these data then could be filtered to the physicians or drug regulatory bodies as CDS or comparative safety/effectiveness profiles of drugs, respectively.

"Ultimately, the benefits reaped from IT systems will always come down to the physicians' willingness to input the appropriate information about their decision making," Walton says. This input may require a helpful nudge from a CMIO.

Last updated on June 28, 2012 at 12:48 pm EST

The Medical Post

MDs should think twice about 'risky' prescribing

Quebec study finds 11% of drugs are prescribed off-label

Written by Mark Cardwell on May 4, 2012 for The Medical Post

It isn't the high number of off-label prescriptions being written by Quebec doctors that most surprises Dr. Tewodros Eguale. It's the fact that so many are for scientifically unproven indications using powerful new drugs.

"Prescribing for indications beyond the safety profile of new drugs isn't a good idea," said the McGill University researcher and lead author in a new study on the off-label prescribing habits of Quebec primary-care physicians. "It's very risky."

The study was based on data from a feature of Quebec's electronic health record network—called Medical Office of the XXI Century, or MOXXI—that documents and links treatment indications for prescribed drugs.

Dr. Eguale

With funding from the Canadian Institutes of Health Research and contributions from fellow McGill researchers Dr. David Buckeridge, Dr. Nancy Winslade (PharmD), Dr. Andrea Benedetti (PhD), Dr. James Hanley (PhD) and Dr. Robyn Tamblyn (PhD), Dr. Eguale first confirmed the validity of the data the MOXXI network collected.

He then analyzed more than 250,000 prescriptions written for just over 50,000 patients by 113 doctors in Montreal and Quebec City over a four-year period that ended in December 2009.

His findings showed that 11% of drugs were prescribed for an off-label indication.

Notably, more than one-quarter of off-label prescriptions involved central nervous system meds. Two-thirds of anticonvulsants, 44% of antipsychotics and one-third of antidepressants were also found to have been prescribed for off-label indications.

The authors note in the background of their study, which was published online in the American Medical Association's biweekly Archives of Internal Medicine on April 16, that the practice of off-

label prescribing is a suspected factor in preventable adverse drug events. (The study also prompted an editorial, posted the same day, with the headline “What does off-label prescribing really mean?”)

One of the most famous examples occurred in the 1990s when fen-phen—an unapproved combination of fenfluramine and phentermine used to treat obesity that the U.S. media dubbed the “Fen-Phen Cocktail”—was found to cause potentially fatal pulmonary hypertension and heart valve problems. The clinical findings led to a wave of liability lawsuits and damage payouts of more than $14 billion.

“Likewise,” the study reads, “when tiagabine, a drug approved to treat seizures, was used off-label to treat conditions like pain, the drug induced seizures.”

The results also suggested that drugs with three or four approved indications were less likely to be prescribed for off-label use than meds with only one or two approved indications. Similarly, medications approved before 1981 were found to be prescribed more for off-label use than drugs approved after 1995.

A physician in his native Ethiopia who came to Canada to study, Dr. Eguale stayed to raise his young family and would like to one day get his medical license here so he can practice in his adopted country.

Dr. Eguale said he understands why physicians seem so quick to write off-label prescriptions for indications in older drugs that are supported by strong evidence in medical circles. But he questions both the sources and the validity of the information on which doctors who write off-label prescriptions are basing their judgment.

THE GLOBE AND MAIL

Editorials

GLOBE EDITORIAL

Lack of research tracking the risks of prescribing drugs "off-label" in Canada

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Prescribing drugs "off-label" – for an ailment or condition they were not meant for – is a quite common practice that has sparked worries about harm to patients and doubts whether they are aware of the risks. Immediate steps need to be taken to make sure doctors have access to a database educating them about what they prescribe.

A study by McGill University researchers in Montreal has concluded that 11 per cent of prescriptions are off-label, used to treat a condition other than one that has been approved by Health Canada for safety and efficacy. Only one in five of the drugs prescribed off-label had some scientific support.

In other words, 79 per cent of such prescriptions lacked strong scientific evidence, according to the study published online last week in Archives of Internal Medicine by Tewodros Eguale, Robyn Tamblyn and their colleagues. It should not only prompt patients to be more aware of their medical conditions but also to discuss their prescriptions with their doctors, said Dr. Eguale.

"What we need are more informed physicians, but at the same time, we need to inform patients," said Dr. Eguale, who analyzed electronic health records of 113 primary-care physicians treating 50,823 patients in Quebec cities between 2005 and 2009.

The drugs most frequently prescribed off-label include anti-psychotics, antidepressants and anti-epilepsy drugs. Anti-infective agents that kill germs or stop their spread were also prescribed in this way, as were ear, nose and throat medications. Women tended to receive them more than men.

This is no neutral matter. Antipsychotics, for example, have been prescribed broadly in nursing homes as a form of chemical restraint for dementia patients. Consequently, Health Canada has issued a warning they can be deadly for that group.

With so many medications on the market – there are about 1,000 of them – it can be challenging for physicians to stay on top of all their uses and guidelines. For that reason, a computerized system that can inform doctors of the best drugs for a given condition should be created and made available across Canada.

As the United States does, Health Canada should move to track off-label use of drugs, with an eye to educating both the profession and patients on these worrisome prescribing patterns.

MACLEAN'S

Off-label drugs are off the charts in Canada

One in 10 pills swallowed is for unapproved use, with little science to back it. No one is keeping track.

by Kate Lunau on Tuesday, May 29, 2012 9:44am -

Photograph by Andrew Tolson

When Rachel Lavallee's son Sam was born five years ago, she was determined to breastfeed, despite a low milk supply. She spoke to her doctor about domperidone—a drug prescribed to treat stomach ailments, that has been used for at least 30 years to help women boost milk production. "It just about doubled my milk supply," says Lavallee, 32, a nurse in Halifax. When son Alex was born last August, she took it again. "For baby number two, it was the same," she says.

This March, Health Canada issued an advisory, stating the risk of abnormal heart rhythms or sudden death may be higher in patients taking higher doses of domperidone, or in those over age 60, based on two new studies. A letter from the Canadian Lactation Consultant Association noted the average age of patients in the studies was 72 and 79, respectively. "When I looked at the [studies] it was based on, it has nothing to do with new mothers," says Joan Fisher, a lactation consultant in Ottawa. Lavallee, who takes three tablets four times a day, is unfazed. "Based on my age, health, and my reasons for taking it, I feel the benefits outweigh the risks." After discussing it with her family doctor, she continues to take the drug. Countless other women are doing the same.

When doctors prescribe domperidone to increase milk production, it's an off-label use, meaning it hasn't been approved by Health Canada. It's not the only drug used this way. Quinine, an anti-malaria medication, has long been prescribed to treat nighttime leg cramps; antipsychotic drugs are frequently given to dampen some symptoms of dementia. At Apex Compounding Pharmacy in Toronto, pharmacist-owner Ara Papazian has raspberry-flavoured lollipops laced with ketamine, a powerful anaesthetic prescribed to those who suffer from chronic pain. "We make Viagra in a

lozenge. As opposed to the guy taking a pill one hour before the act, he can pop this under his tongue and he's good to go within 15 minutes." Papazian sometimes recommends an anti-cancer drug, tamoxifen, in an ointment to help heal scars.

Prescribing off label is accepted medical practice, one that allows doctors to tailor treatments to patients who may not benefit from other forms of medication. But it carries risks. "When you go off label, one has to be really cautious," says Dr. Tewodros Eguale of McGill University, lead author of a new paper that looks at how common these prescriptions are. "It's not always well known whether it will give you a severe reaction." It's such standard practice that doctors often don't even realize they're doing it: one 2009 study asked 1,200 U.S. psychiatrists and primary care doctors to look through a list of medical conditions and the drugs used to treat them. They identified whether the use was approved roughly half the time.

Eguale's study, published in the *Archives of Internal Medicine*, found a little more than one in 10 drugs were prescribed off label. Using electronic health records, he and his co-authors looked at a total of 253,347 prescriptions in Quebec from 2005 to 2009 for more than 50,000 adult patients. Of the drugs prescribed off label, 79 per cent "lacked scientific evidence" that the treatment would work. Drugs that affect the central nervous system—like antipsychotics and antidepressants—were most often prescribed for an off-label use. Interestingly, women were more likely to get off-label prescriptions because they're more often treated for conditions like anxiety and insomnia, where off-label prescribing is common. In a separate study of prescribing in the U.S., researchers found that 21 per cent of prescriptions were for off-label uses, and of that number, 72 per cent had "uncertain or inadequate" evidence the prescription would work.

"It's a benefit-risk calculation for the physician," Eguale says. In the case of quinine, "there's no effective drug to treat nocturnal leg pain," so doctors prescribe the anti-malaria drug, which has a long history of being used this way, although it isn't approved for that use in Canada or the U.S. In April 2011, Health Canada issued an advisory that, as of the previous September, it had received 71 reports of serious adverse reactions related to quinine sulfate—41 of them were life-threatening or required hospital admission. "Only four of the 71 reports listed malaria as the indication for use of the drug," it says. The remaining 67 were all for cramps. The letter concludes with a reminder that quinine sulfate "is not indicated for the prevention or treatment of nocturnal leg cramps."

It seems bizarre that an anti-nausea drug could help breastfeeding, or a malaria fighter might help subdue leg cramps. But that's the story of drug development, Papazian says. Sometimes a drug's side effects are more beneficial than its intended purpose. Viagra was initially developed as a cardiac drug, but then manufacturer Pfizer Inc. realized it could induce erections. The first oral pill to treat impotence was approved by the U.S. Food and Drug Administration (FDA) in 1998. "Pfizer went on to make a fortune based on a side effect," Papazian says.

Even though a drug's side effects can be profitable, as Viagra shows, there are plenty of reasons a drug company might not bother seeking regulatory approval of off-label uses. "It's very expensive to pull data together and present it to Health Canada or the FDA," Eguale says. "If a drug is old and its patent is about to expire, the pharmaceutical companies won't bother." And if side effects promise to help only a small segment of the population, it might not be worthwhile either.

Children are often prescribed medication off label because, for ethical and other reasons, companies have historically been reluctant to include them in clinical trials, says Dr. Randall Stafford, associate professor of medicine at the Stanford Prevention Research Center and co-author of the U.S. study on off-label prescribing. "But many would argue that if a drug is going to enter the market and be used in children, there's an obligation to test it," Stafford says. The FDA

has started offering incentives to do studies in children, like a longer period of market exclusivity—meaning companies would have more time without having to face competition with generics.

Once a drug is approved, doctors are free to prescribe it based on its official use, a scientific paper, a conversation with a colleague, or even a hunch. If Papazian encounters a doctor who's hesitant to try a drug off label, and the pharmacist believes it could help, "I'll fax him the latest research to convince him," Papazian says. "Nine times out of 10, the doctor says yes." Even though drug companies profit from the off-label use of their products, they aren't allowed to advertise unofficial uses. But many have found ways to do it anyway—and have faced hefty fines when caught.

In 2009, Pfizer was charged $1.19 billion, the largest health care fraud settlement in U.S. history, for promoting the anti-inflammatory drug Bextra to treat pains of all kinds, at dosages the FDA never approved (it was pulled from the market in 2005). It illegally promoted three other drugs, too. In 2004, Warner-Lambert, which merged with Pfizer in 2000, pleaded guilty and agreed to pay more than $430 million to resolve criminal charges and civil liabilities after promoting epilepsy drug Neurontin to treat everything from bipolar disorder to migraines to restless leg syndrome.

In some cases, off-label use becomes standard, like Aspirin for patients at high risk of coronary artery disease. Dr. Joel Lexchin, a professor of health policy at York University who's also worked as an emergency room doctor for 30 years, says he sometimes sees people with headaches "that have a particular trigger point. You press one point in the back of their head, typically where the muscles go into the skull, and they say, 'That really hurts.' So you take a bit of lidocaine freezing and inject it into that spot. A couple of millilitres of lidocaine isn't going to do any harm, unless they're allergic." In other cases, when off-label drugs are prescribed for long periods of time or carry significant side effects, "you really would worry about [prescribing it]. At least, I would," he says.

The use of antipsychotics to treat symptoms of dementia has been especially controversial. "They are prescribed very frequently, too frequently," says Dr. Nathan Herrmann, head of geriatric psychiatry at Sunnybrook Health Sciences Centre and a professor in the University of Toronto's faculty of medicine. "They do reduce the agitation, aggression and psychotic symptoms, like hallucinations and delusions," but they can have harmful side effects, including an increased risk of stroke and mortality. Beyond that, "they can be very sedating. They cause movement disorders. They can make memory and other cognitive functions worse."

Antipsychotics have been used this way for decades, and for now, they're still sometimes the best option, Herrmann says—but they should only be doled out for severe problems, like aggression or psychosis, when the patient might harm themselves or others. "Some people are getting them for mild anxiety, or to help with sleep, or because they're shouting," which is inappropriate, he says. According to Lexchin, who's preparing a chapter in a forthcoming book about this, studies suggest about one in three patients in Canadian nursing homes are prescribed antipsychotics, almost always off label.

In 2002, following the death of a six-year-old New Brunswick girl, a coroner's jury made a recommendation to Health Canada to formally monitor off-label use of drugs. (The anaesthetic in question in the case, propofol, was ruled out as the cause of death.) Health Canada, which regulates drugs, insists it can't control what doctors prescribe, a position the FDA also maintains. To Stafford and others, this is cause for concern. "It's something that should be monitored," he

says. “When you talk about drugs being used by millions of Americans or Canadians, we’d better be pretty certain what we’re doing.” A shocking number of prescriptions are written on hazy evidence. “Although some drugs prescribed off label are done so appropriately,” Lexchin says, “most of the off-label prescribing in Canada doesn’t have a scientific basis.”

Monitoring would have many benefits, Lexchin notes: We might be able to pinpoint beneficial uses for drugs that are currently unapproved. We might get a better idea of the harmful effects of others. Until patients across Canada have electronic health records, for one thing, it’s unlikely we’ll be able to do a very good job tracking it, even if Health Canada did take on that role.

If domperidone was officially approved to boost breast milk production, Lavallee says that would be ideal. For those taking off-label drugs, it can feel like a gamble, but for moms nursing new babies, it is one many are willing to take.

REUTERS

Study finds high rates of off-label prescribing

Thu Apr 19, 2012 4:21pm EDT

By Andrew M. Seaman

NEW YORK (Reuters Health) - More than 10 percent of prescriptions in one Canadian province were for drugs not approved to treat the patient's condition, a new study finds. And many times, there was little evidence the drugs would work.

A medication is being used "off label" if a doctor prescribes it to treat a condition other than the one(s) Health Canada, the U.S. Food and Drug Administration or similar national regulatory agencies approved it for based on tests of safety and efficacy.

Dr. Tewodros Eguale, who led the new study, said doctors typically prescribe medications off-label when their patients fail to respond to other popular approved drugs or when they have a rare condition with few available treatments.

Eguale, from McGill University in Montreal, and his colleagues used data on every prescription written by Quebec physicians participating in an electronic health record network. The network is unusual in that it requires a doctor to state what the prescribed drug is intended to treat.

Between 2005 and 2010, 113 primary care doctors wrote more than 250,000 prescriptions for just over 50,000 patients.

Eleven percent of those prescriptions were considered off-label by the standards of the Health Canada drug database.

The researchers didn't have information on how well those drugs ended up working for the patients who took them. But they determined that four out of five off-label prescriptions didn't have strong evidence suggesting they were likely to be effective.

"Strong evidence" in this case included at least one controlled clinical trial -- considered the "gold standard" of medical research - showing the drug could help the patient's disorder.

Drugs meant to treat central nervous system conditions, like chronic pain, as well as infections and ear, nose and throat problems were most likely to be prescribed off-label.

The researchers also found that drugs approved by the Canadian government prior to 1981 were much more likely to be prescribed off-label than modern drugs.

Eguale told Reuters Health that not being approved for a specific condition doesn't mean a medication won't work, or that it's not safe.

Just as with newly-approved drugs, he said, "one has to be cautious. If you're giving it for off-label indications, you have to be careful about safety."

In an editorial accompanying the new study, published in the Archives of Internal Medicine, Dr. Patrick O'Malley wrote that unless pharmaceutical companies believe they can make a profit, they probably won't try to get new approvals for a drug even if its (off-label) use is widely accepted.

Getting a drug approved for specific conditions can be onerous and require lots of financial risk, according to O'Malley, an internist at the Uniformed Services University of the Health Sciences in Bethesda, Maryland.

The current U.S. research infrastructure would not be able to test whether every drug is appropriate for every known condition, according to O'Malley.

So there's no way to know whether the 11 percent of drugs used off-label in the new study is too much or too little, he said -- but there are things doctors can do to make sure they're using such drugs appropriately.

"Doctors should first be very clear about what evidence is available for that treatment, and they should be informing patients," he told Reuters Health.

Eguale and his colleagues found that physicians who said they practiced evidenced-based medicine were less likely to prescribe medication off-label.

And, Eguale said, making sure drugs are properly prescribed goes beyond just the physician.

"I think we need an informed physician, but we need an informed patient as well," he said.

The study did have certain limitations, the researchers note, including that the definition of "off-label" may have differed depending on how much of a drug was prescribed. And some apparently off-label use could have been explained by other conditions not included in a patient's electronic record.

The study also only looked at one province in Canada, which means the results may not be true for other areas of the country or in other countries.

But O'Malley said he suspects the results would not be that different in the U.S.

SOURCE: bit.ly/Iz1FSJ and bit.ly/IRzmCt Archives of Internal Medicine, online April 16, 2012.

CBC

Off-label drug use reaches 11%

CBC News

Posted: Apr 17, 2012 10:05 AM ET

Read 59comments59

Doctors often prescribe a drug for conditions other than what it was originally meant to treat, a Quebec study finds.

Prescription drugs are given off label for purposes or groups of patients that regulatory agencies like Health Canada haven't officially approved, such as prescribing medication for anxiety to someone with insomnia.

The researchers worry that off-label prescribing can lead to adverse events. A classic example was the appetite suppressor fen-phen, which could cause serious cardiac valve damage when prescribed off label for weight loss.

Off-label prescribing can be a sign of inappropriate use.(Associated Press)

"The prevalence of off-label use was 11 per cent," Dr. Tewodros Eguale of McGill University and his co-authors concluded in Monday's online issue of the Archives of Internal Medicine. "Of off-label prescriptions, 79 per cent lacked strong scientific evidence."

To come to that conclusion, the researchers checked into off-label drug use by analyzing electronic health records for 113 primary care physicians treating 50,823 patients in Quebec cities between 2005 and 2009.

To use the electronic records, doctors had to say why they were prescribing a medication, which allowed the researchers to link prescribed drugs to conditions and the characteristics of the patients.

The types of drugs that were prescribed off-label most often included:

Central nervous system drugs such as neurogenic pain medications like gabapentin, the antidepressant amitripyline and anti-epilepsy medication topiramate.

Anti-infective agents that kill germs or stop their spread.

Ear-nose-throat-medications.

The highest proportion of off-label prescriptions were for central nervous system drugs.

The researchers pointed to a doctor's lack of knowledge about drugs and the scarcity of approved or effective drugs as possible reasons driving off-label prescribing.

Women received more off-label prescriptions than men because they were more likely to be treated for problems where the practice is common, such as anxiety, nocturnal leg pain and insomnia.

Doctors try 'what seems reasonable'

Older drugs were also prescribed off label more. Since those medications were on the market for longer, there were more opportunities for doctors to discover new uses, the study's authors said.

Also, when a drug goes off-patent, the manufacturer is unlikely to apply to regulators for a new purpose.

It's important to consider the strength of evidence to judge if inappropriate prescribing is occurring, said Dr. Patrick O'Malley of the Uniformed Services University of the Health Sciences in Bethesda, Md. in a journal editorial published with the study.

"The reality is that when faced with difficult symptom syndromes that are unresponsive to available treatments, clinicians resort to trying what seems reasonable in order to alleviate suffering," O'Malley said.

He called for better tracking of medications by diagnosis and appropriateness, instead of making decisions based on clinical trial results or guidelines.

The study was funded by the Canadian Institutes of Health Research.

Medscape

CNS Drugs Most Often Prescribed Off-Label

Fran Lowry

April 18, 2012 — Primary care physicians commonly prescribe drugs, especially central nervous system (CNS) agents, for indications that have not received regulatory approval, a new study shows.

Drugs with the highest prevalence of off-label use were anticonvulsants, antipsychotics, and antidepressants, researchers report.

"Female patients, and those who are healthier, were more likely to receive off-label prescriptions than male, and sicker individuals," lead author Tewodros Eguale, MD, MSc, from McGill University, Montreal, Quebec, Canada, told *Medscape Medical News*. "That makes sense. If you are going to experiment, it is better to do so with healthier patients."

Older drugs, those approved before 1981, were also associated with more off-label use than were drugs approved after 1995, and physicians who favored evidence-based medicine tended to prescribe less off-label drugs, he said.

Their findings are published online April 16 in the *Archives of Internal Medicine*.

Mandatory Indication

Dr. Eguale and his team used the Medical Office of the XXI Century electronic health record system in the province of Quebec to examine off-label use.

"In this system, it is mandatory that the doctors put in a treatment indication for every drug they prescribe. The indication can be on-label or off-label, and the doctors also have the opportunity to write whether the indication is unlisted, so there is a direct link between the drug and the indication," Dr. Eguale explained. "To our knowledge, this study is the first to take advantage of the mandatory inclusion of this important information."

The system has been in place in Quebec since 2005.

A total of 113 primary care physicians wrote 253,347 electronic prescriptions for 50,823 patients aged 18 to 100 years from January 2005 through December 2009.

The researchers found that overall, the prevalence of off-label use was 11.0%. Of these off-label prescriptions, 79.0% lacked strong scientific evidence.

Off-label prescribing varied among the classes of drugs. Central nervous system drugs had the highest prevalence of off-label use (26.3%). Among the CNS drugs most prescribed off label were anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%).

Specific drugs with the highest off-label use included quinine sulphate (99.5% of prescriptions), followed by gabapentin (99.2%), clonazepam (96.2%), amitriptyline hydrochloride (93.7%), trazodone hydrochloride (92.6%), and betahistine dihydrochloride (91.5%).

Anti-infective agents had the second highest proportion of off-label prescribing (17.1%), followed by ear, nose, and throat medications (15.2%).

Antidiabetes drugs (0% - 2%), lipid-lowering drugs (0% - 0.5%), and antimigraine drugs (0%) had the lowest prevalence of off-label use.

The study also found that women received more off-label drugs than men (11.8% vs 9.7%, adjusted odds ratio [AOR], 1.06; 95% confidence interval [CI], 1.03 - 1.09). "This is probably because women were more likely to be treated for problems such as anxiety, nocturnal leg pain, and insomnia, and off-label prescribing is common for these conditions," Dr. Eguale explained.

Physicians who favored evidence-based medical practice were less likely to prescribe off-label than those who did not (AOR, 0.93; 95% CI, 0.88 - 0.99). "This is a very interesting finding," Dr. Eguale said. "Nobody has really tried to look at off-label prescribing and this physician characteristic of favoring or not favoring evidence-based medicine before."

The next step is to determine whether off-label prescribing causes harm and the reasons why patients were told to stop taking their medication, Dr. Eguale said.

"We want to determine if the off-label drugs were effective or ineffective, whether they caused adverse reactions, and why they were stopped. Our goal is to bring about a new type of pharmacosurveillance," he said. "Right now, we have spontaneous reporting of adverse drug reactions but it is well known that only 1% to 10% of those reactions are reported. By using this electronic medical record system, we can capture if not all, most of the outcomes that occur with the drugs."

Appropriate and Rational

In an accompanying editorial, Patrick G. O'Malley, MD, MPH, from the Uniformed Services University of the Health Sciences, Bethesda, Maryland, writes: "The principles and goals of labeling are worthy in that they seek to systematically identify the benefits and harms associated with drugs in order to allow the public to optimize the trade-off between drug risk and harm. However, there is substantial room to grow in realizing these ideals in practice."

Dr. O'Malley notes that the meaning of off-label use "depends on the perspective, especially in areas in which the evidence is lagging. For the practicing clinician who is faced with a suffering complex patient for whom there is no evidence-based treatment, it may be entirely appropriate and rational to extrapolate the efficacy of a treatment for one condition to another."

He concludes with his view about finding a way to go forward on this topic. "First, the discourse needs to focus less on overuse or underuse or off-label use and more on evolving toward better measurement of use, better assessment of appropriate use based on linkage to clinical outcomes, and better processes to optimize use."

The study was funded by a grant from the Canadian Institutes of Health Research. Dr. Eguale and Dr. O'Malley have disclosed no relevant financial relationships.

One in 9 drugs prescribed in Que. are 'off-label': study

The Canadian Press
Published Tuesday, Apr. 17, 2012 8:00AM EDT

TORONTO - One out of every nine prescriptions written in Quebec is for a drug that isn't being used for the purposes for which it was licensed, a new study suggests.

That practice is called off-label use. Doctors may give a drug approved for anxiety to patients who are looking for help with insomnia. It's a common practice, though one that can lead to dangerous use at times. But it's very hard to quantify.

Now researchers at McGill University have used a database of over a quarter-million prescriptions written for 51,000 patients to look at this issue. The data are drawn from an electronic medical records system devised at McGill and used by a group of physicians in Montreal and Quebec City.

The system requires doctors not just to register prescriptions they are giving to their patients, but to list the condition for which the drug is being prescribed. And that allows researchers like the team led by Dr. Tewodros Eguale to study what drugs are being prescribed for which conditions and whether there is any evidence that the drug actually works for the ailment in question.

The study was published Monday on the website of the journal *Archives of Internal Medicine.*

"Everybody talks about it but the problem is it's very difficult to measure off-label prescribing with the current methods," Eguale said in an interview from Montreal.

"In our study we are not saying that off-label prescribing is really harmful. That's why we went and looked at whether there is any evidence, strong evidence, for its use."

He and his colleagues found that 11 per cent of prescriptions written by 113 doctors from 2005 through 2009 were for off-label uses.

And in nearly 80 per cent of the cases where off-label prescriptions were written, there was no strong evidence to suggest the drug would work for the problem ailing the patient who got the prescription.

Older drugs -- those approved before 1981 -- were more likely to be used off label than newer medications.

One reason for that may be that even if there is a belief an existing drug might be useful for condition X or Y, if it's not covered by a patent drug companies are unlikely to pony up the huge sums it takes to do the trials needed to get a new indication -- approved use -- added to a drug's label.

Eguale said an off-label use can evolve in situations where there is a need for treatment, but no proven effective drug.

"There is a tendency for physicians to experiment or with very small randomized controlled trials with a small number of patients, they may be convinced to try it," he explained.

Then word seems to spread and one person's experiment may become more broadly used.

"Whenever the pharmaceutical companies are not involved, I think this is mostly the way this kind of information is propagated," Eguale said.

Off-label prescribing can be useful, said Dr. Muhammad Mamdani, a pharmacist and director of the Applied Health Research Centre at the Li Ka Shing Knowledge Institute of Toronto's St. Michael's Hospital. Mamdani was not part of the study.

But other times, the use of a drug for a condition it hasn't been tested for is dangerous. Mamdani pointed to the use of human growth hormone by athletes as an example.

"Off-label use can be harmful, but it may also in some cases help patients -- we simply don't know since there is typically a lack of evidence," he said.

"So it's often difficult to tell whether a particular off-label use of a drug is helping or harming the patient. On the conservative side, I think most people assume it will harm the patient."

RADIO-CANADA

Beaucoup de prescriptions « hors normes » au Québec

Mise à jour le mercredi 18 avril 2012 à 11 h 04 HAE

La prescription non conforme de médicaments par les médecins de premier recours semble être une pratique répandue au Québec, montre une étude effectuée à l'Université McGill.

Le Dr Tewodros Eguale et ses collègues ont constaté que 11 % des ordonnances rédigées par une centaine de médecins de première ligne au Québec dérogeaient aux directives indiquées sur l'étiquette du médicament et pour lesquelles celui-ci a été approuvé par Santé Canada.

Cette pratique est particulièrement répandue pour les médicaments qui traitent le système nerveux (26 %), comme les anticonvulsifs, les antidépresseurs et les antipsychotiques. Les anti-infectieux sont également l'objet de ce type de prescription (17 %).

De plus, les médicaments qui comptent trois ou quatre indications approuvées étaient moins souvent employés de façon non conforme que ceux qui n'en comptaient qu'une ou deux. Ceux homologués après 1995 étaient aussi associés à une utilisation hors indications moins fréquente.

« Les résultats de notre étude indiquent que la prescription non conforme de médicaments est une pratique répandue chez les médecins de premier recours, mais que sa fréquence varie selon la classe et l'âge du médicament, le nombre d'indications approuvées, le sexe du patient et l'importance accordée à la médecine factuelle. » — *Auteurs*

Le Dr Eguale affirme que la prochaine étape consiste à établir des liens entre les médicaments et leurs indications, d'une part, et les résultats thérapeutiques d'autre part. Selon lui, il sera ainsi possible de déterminer si le médicament améliore l'état du patient ou s'il entraîne des effets néfastes.

Le détail de cette étude est publié dans les *Archives of Internal Medicine*.

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