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

Tewodros Eguale,[1] *Robyn Tamblyn*,[1,2] *Nancy Winslade*[1] and *David Buckeridge*[1]

1 Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
2 Department of Medicine, McGill University, Montreal, Quebec, Canada

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

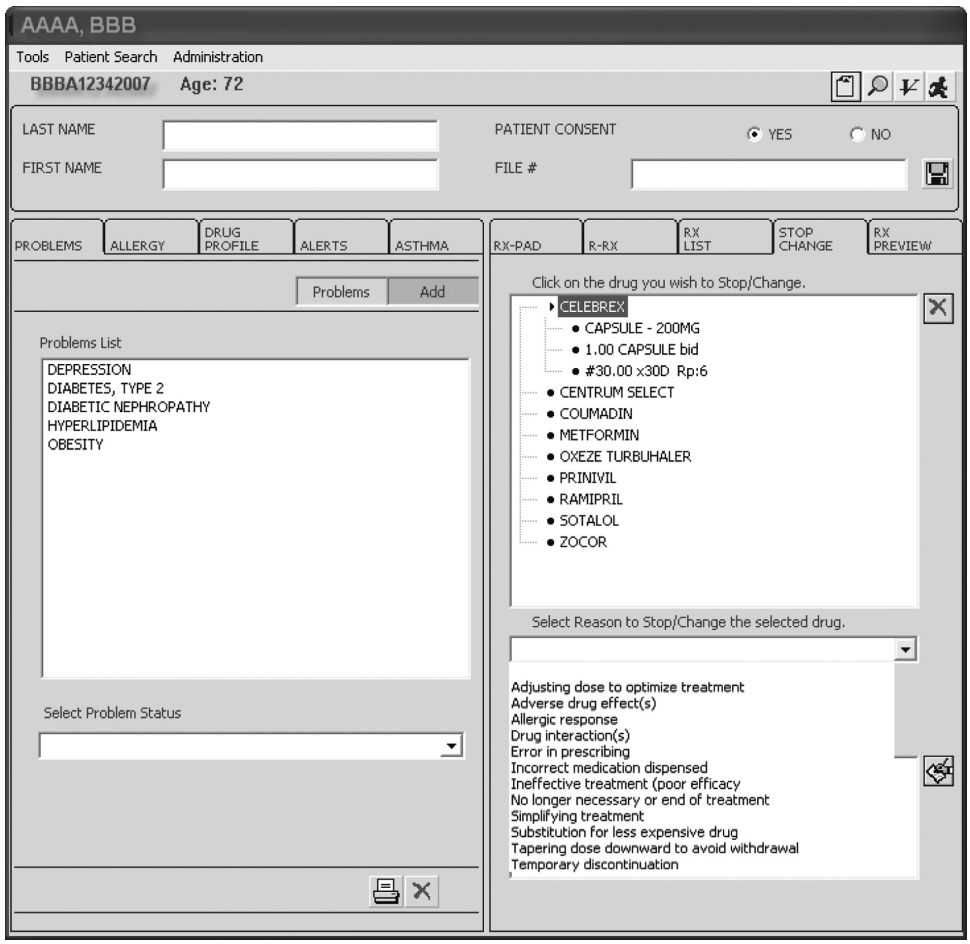

Fig. 1. Drug discontinuation and dose-change feature of the Medical Office for the XXI century prescribing and drug management system.

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).

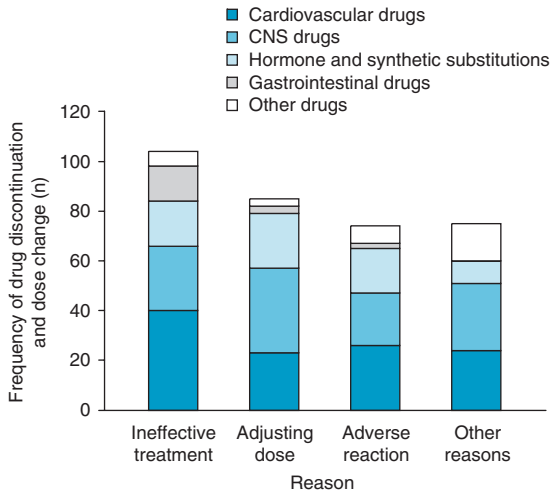

Fig. 2. Frequency distribution of drug discontinuation and dose change by drug class and by the reason for discontinuation or change.

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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Correspondence: Dr *Tewodros Eguale*, Clinical and Health informatics research group, McGill University, 1140 Pine Avenue West, Montreal, QC H3A 1A3, Canada.
E-mail: tewodros.eguale@mail.mcgill.ca