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

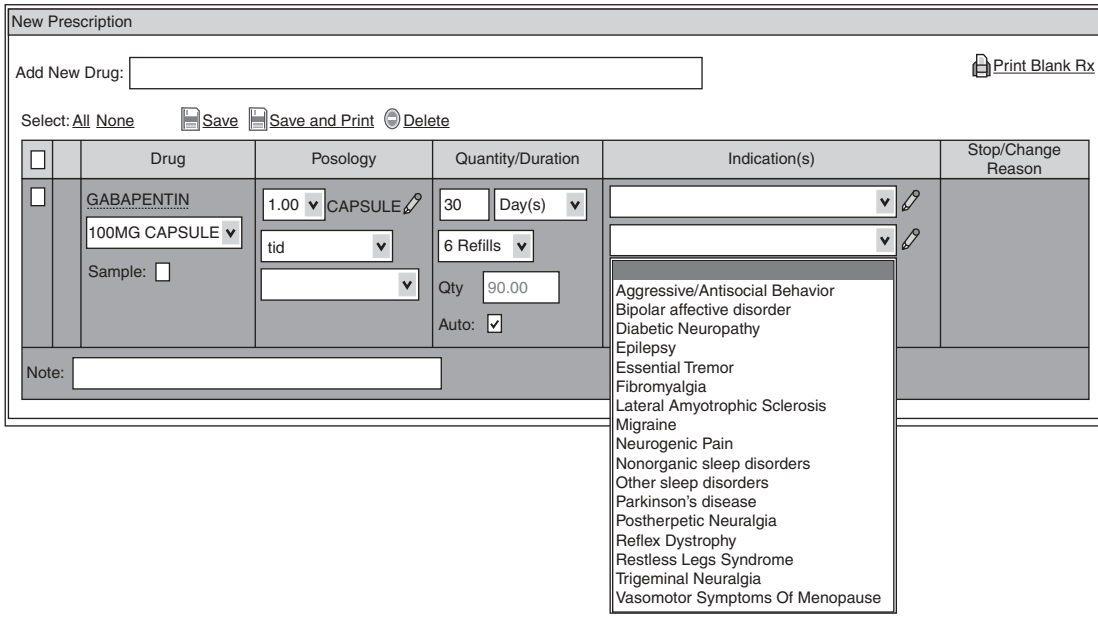

Fig. 1. Documentation of treatment indication in the Medical Office for the XXI century (MOXXI) system.

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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