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-

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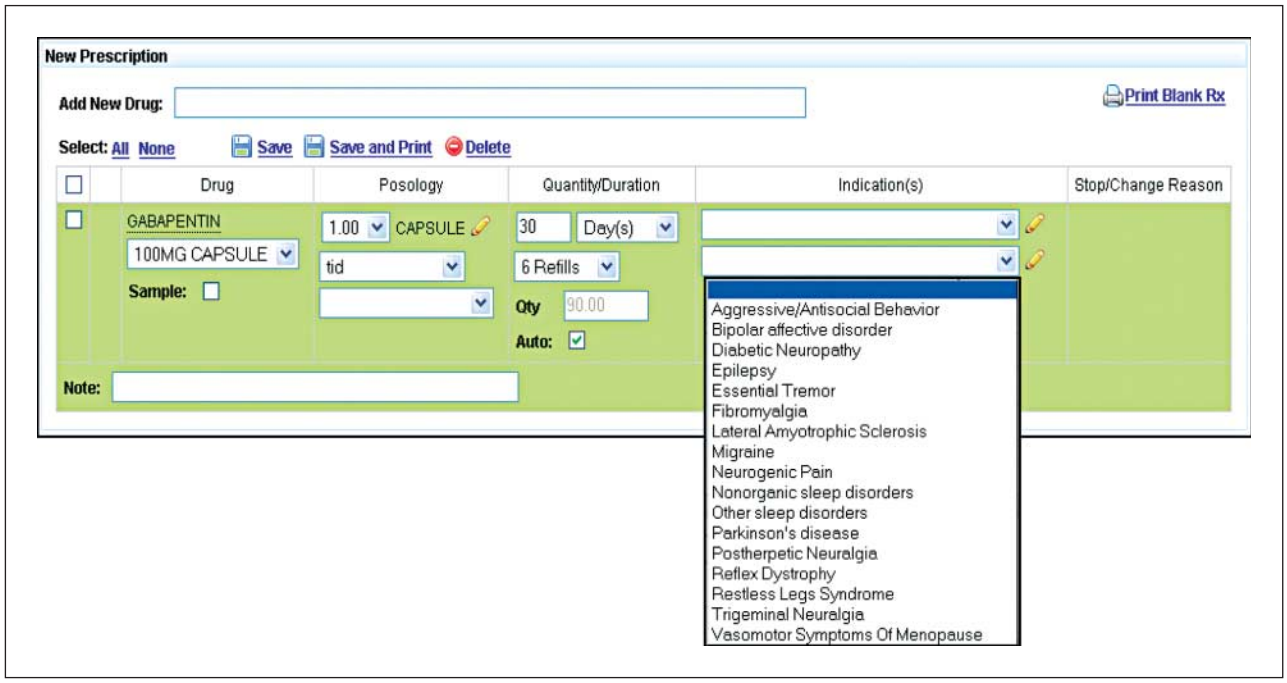

Figure 1. Documentation of treatment indication in the Medical Office of the XXI Century electronic prescribing system.

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]

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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.

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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.

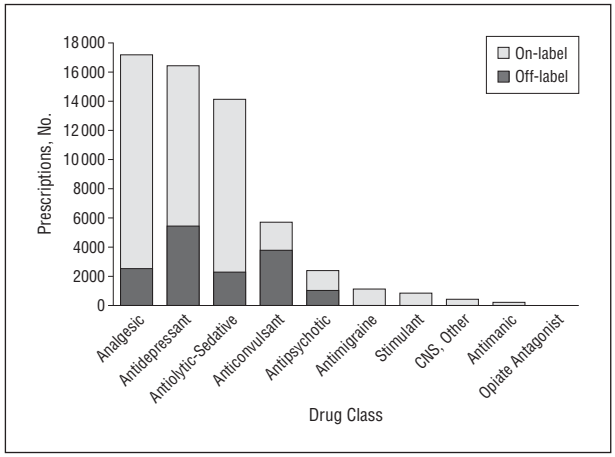

Figure 2. Frequency distribution of central nervous system (CNS) drugs by drug approval status (on-label and off-label).

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

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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-

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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-

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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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