**Original Investigation | HEALTH CARE REFORM**

**Association of Off-label Drug Use and Adverse Drug Events in an Adult Population**

Tewodros Eguale, MD, PhD; David L. Buckeridge, MD, PhD; Aman Verma, PhD; Nancy E. Winslade, PharmD; Andrea Benedetti, PhD; James A. Hanley, PhD; Robyn Tamblyn, PhD

**IMPORTANCE**  Off-label use of prescription drugs has been identified as an important contributor to preventable adverse drug events (ADEs) in children. Despite concerns regarding adverse outcomes, to date, no systematic investigation of the effects of off-label drug use in adult populations has been performed.

**OBJECTIVE**  To monitor and evaluate off-label use of prescription drugs and its effect on ADEs in an adult population.

**DESIGN, SETTING, AND PARTICIPANTS**  A cohort of 46,021 patients who received 151,305 incident prescribed drugs was assembled from primary care clinics in Quebec, Canada, using the Medical Office of the XXIst Century electronic health record, which supports documentation of treatment indications and treatment outcomes. Prescriptions dispensed from January 1, 2005, through December 30, 2009, were followed up from the date of the prescription to the date the drug use was discontinued, the end of treatment, or the end of follow-up (December 30, 2010). Data were analyzed from January 5, 2012, to March 15, 2015.

**EXPOSURES**  Off-label prescription drug use with and without strong scientific evidence.

**MAIN OUTCOMES AND MEASURES**  Adverse drug events in off-label use with and without strong scientific evidence. Analysis used multivariate marginal Cox proportional hazards regression for clustered data with the drug as the unit of analysis.

**RESULTS**  A total of 3,484 ADEs were found in the 46,021 study patients, with an incidence rate of 13.2 per 10,000 person-months. The rate of ADEs for off-label use (19.7 per 10,000 person-months) was higher than that for on-label use (12.5 per 10,000 person-months) (adjusted hazard ratio [AHR], 1.44; 95% CI, 1.30-1.60). Off-label use lacking strong scientific evidence had a higher ADE rate (21.7 per 10,000 person-months) compared with on-label use (AHR, 1.54; 95% CI, 1.37-1.72). However, off-label use with strong scientific evidence had the same risk for ADEs as on-label use (AHR, 1.10; 95% CI, 0.88-1.38). The risks for ADEs were higher for drugs approved from 1981 to 1995 (14.4 per 10,000 person-months; AHR, 1.62; 95% CI, 1.45-1.80) and for those used by women (14.3 per 10,000 person-months; AHR, 1.17; 95% CI, 1.06-1.28), patients receiving 5 to 7 drugs (12.1 per 10,000 person-months; AHR, 3.23; 95% CI, 2.66-3.92), and patients receiving cardiovascular drugs (15.9 per 10,000 person-months; AHR, 3.30; 95% CI, 2.67-4.08) and anti-infectives (66.2 per 10,000 person-months; AHR, 6.33; 95% CI, 4.58-8.76). Patients with a 1-unit increase in the continuity of care index had a 19% increase in ADEs (AHR, 1.19; 95% CI, 1.12-1.26).

**CONCLUSIONS AND RELEVANCE**  Off-label use of prescription drugs is associated with ADEs. Caution should be exercised in prescribing drugs for off-label uses that lack strong scientific evidence. Future electronic health records should be designed to enable postmarket surveillance of treatment indications and treatment outcomes to monitor the safety of on- and off-label uses of drugs.

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Off-label prescribing of drugs is common\(^1\) and has been identified as a potentially important contributor to preventable adverse drug events (ADEs). Significant deleterious effects can occur with off-label use of some drugs, such as cardiac valve damage with fenfluramine and phentermine (fen-phen),\(^3\) status epilepticus with tiagabine hydrochloride,\(^4\) thrombocytopenia with quinine sulfate,\(^5\) and thromboembolic events with recombinant factor VIIa.\(^6\)\(^,\)\(^7\) Despite concerns about adverse outcomes, no systematic investigation of the effect of real-life off-label use on adverse events has been performed.

The Institute of Medicine and drug regulatory agencies have envisioned a postmarket surveillance system in which patterns of drug use, indications for the use (on- and off-label), and associated ADEs could be tracked.\(^8\)\(^-\)\(^10\) However, an explicit link between prescribed drugs and their indication is rarely documented, making it challenging to measure off-label use and its effects.\(^11\) Recently, methods to support the documentation of treatment indication, reasons for discontinuation of treatment orders, and ADEs have been developed, and evidence supports requiring these elements in electronic prescription.\(^12\)\(^,\)\(^13\) These new features provide a unique opportunity to monitor and evaluate off-label use and its effect on ADEs systematically. The results from such monitoring can provide important guidance to initiatives aimed at regulating off-label use and strengthening the role of drug regulatory bodies (eg, the US Food and Drug Administration and Health Canada).\(^14\)\(^,\)\(^15\)

### Methods

**Context**

The study was conducted in Quebec, Canada, a province that provides health insurance for all 8.5 million residents. In 2003, the Medical Office of the 21st Century (MOXXI), a community-based clinical information system, was created to link beneficiaries, medical billing, and pharmacy claim data to create a longitudinal electronic health record (EHR) for patients.\(^16\) Evidence of validity for the data has been shown, and these data have been used frequently for health services and epidemiologic research.\(^17\) One hundred thirteen primary care physicians participate in the MOXXI research program, and these physicians work in office-based practices in Montreal or Quebec City. The MOXXI data overrepresent older patients and patients with frequent physician visits.\(^16\)

In the MOXXI EHR, physicians must document the treatment indication for each new electronic prescription, the reasons for dose changes and drug discontinuation orders, and the nature of any ADEs (Figure 1 and eFigure in the Supplement). After a new prescription is entered through the MOXXI system, the patient may fill the prescription at a pharmacy and may experience an ADE. At the next visit to a MOXXI physician, if the prescription is not renewed, the reason for discontinuation must be documented within the MOXXI system. In this way, the reasons for all discontinuations of drug use are recorded. The reasons for discontinuation are grouped into the following 5 domains: safety (eg, adverse drug reaction, allergic response, or drug interaction), effectiveness (eg, ineffective treatment, no longer necessary), prescribing or dispensing errors, factors associated with adherence to the medication regimen (eg, simplifying treatment, substitution of a less expensive drug), and factors such as patient request and discontinuations by other physicians. The ADEs are documented using a prepopulated, drug-specific ADE list that is mapped to the Medical Dictionary for Regulatory Activities (MedDRA) classification. Physicians can also search from the global list of ADEs or can use free text to enter a specific ADE description. To support clinical decision making, treatment indications automatically populate the patient’s list of medical problems. Prior failed treatment and reasons for discontinuations of drug treatment (eg, ADE, hypotension) are listed under each indication.

### Design and Study Population

To evaluate the association between off-label use and ADEs, a prospective cohort of 46 021 adult patients (aged ≥18 years) with an incident prescription for a drug was assembled from January 1, 2005, through December 30, 2009. A drug prescription was considered incident if the same drug had not been prescribed or dispensed in the past 12 months. Prescriptions were followed up from the date of the prescription to the date the drug use was discontinued, the end of treatment, or the end of follow-up (December 30, 2010). The MOXXI research program was approved by the institutional review board of McGill University. Patients and physicians provided written informed consent to be part of the research program.

### Adverse Drug Events

**Adverse drug events** were defined as discontinuations of drug use made by physicians owing to an adverse drug reaction or an allergic reaction. Prior evaluation of the validity of these data found an 85.7% concordance between the electronic documentation of ADEs with the medical record.\(^13\) The ADEs were categorized using MedDRA, which includes system organ classes and preferred terms. The system organ classes represent the highest hierarchy that provides the broadest concept for data retrieval and analysis, and preferred terms provide a distinct descriptor of sign, symptom, diagnosis, or surgical or medical procedure.

### Risk for ADEs and Off-label Use

The indication recorded for each prescription was classified as on-label or off-label use according to the Health Canada drug approval database.\(^18\) Compared with the medical record, the sensitivity (completeness) and the positive predictive value (correctness) of the documentation of electronic treatment indication in the MOXXI system were 98.5% and 97.0%, respectively.\(^12\) Indications were considered approved by Health Canada (on-label) if they could be matched to the therapeutic indication reported in the drug’s package insert as of December 2010. Any indication that could not be matched to the labeled indication was considered off-label. For each off-label drug indication, the level of evidence supporting the drug’s overall efficacy was categorized using the DrugPoints System (Thomson Reuters). Strong evidence exists when (1) the drug is effective or favors efficacy for the off-label treatment indication, (2) the drug is recommended for at least most patients with the off-label treatment indication, and (3) the
studies used to evaluate efficacy and the strength of evidence include at least 1 randomized controlled trial.\(^2,19\) Accordingly, we created the following 2 variables: (1) on- or off-label use and (2) off-label use with and without strong scientific evidence. In eTable 1 in the Supplement, we tabulated selected drugs and off-label indications with and without strong scientific evidence.

We measured drug class as a potential risk factor for ADEs because the central nervous system (CNS), cardiovascular, and anti-infective classes were more often implicated in ADEs.\(^20,21\) Drug age, defined as the year the drug was approved for marketing, was included because ADEs were more likely to be reported with recently approved drugs than older drugs.\(^22\) Drug age was categorized into the following 3 groups: before 1981; 1981 through 1995; and after 1995 (recent approval).

For patient characteristics, we included age and measures of comorbidity (Charlson comorbidity index; range, 0-25; 1 or greater indicates increased risk for death)\(^23\) because older patients\(^6,21\) and those with more than 1 comorbidity\(^24\) may have a higher risk for ADEs. Patient sex was included because higher rates of ADEs were reported for women than men.\(^25,26\) The number of drugs the patient was taking was included because it was shown to be the most important risk factor for ADEs.\(^20,27,28\) The continuity of care (COC) index was included to correct for possible surveillance bias in the opportunity to detect ADEs because patients with better continuity have fewer emergent visits,\(^29\) possibly because ADEs and disease exacerbations are more likely to be detected and averted.

The COC index was defined as the ratio of the number of a patient's visits to the primary care physician to the square root of the patient's total outpatient visits and calculated using the medical services claims.\(^30\)

### Statistical Analysis

Data analysis was performed from January 5, 2012, to March 15, 2015. Incidence rates of discontinuations of drug use owo-
Table 1. Drug and Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic (n = 151 305)</th>
<th>Dataa</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-label use</td>
<td>133 458 (88.2)</td>
</tr>
<tr>
<td>Off-label use</td>
<td>17 847 (11.8)</td>
</tr>
<tr>
<td>With strong evidence</td>
<td>3416 (2.3)</td>
</tr>
<tr>
<td>Without strong evidence</td>
<td>14 411 (9.5)</td>
</tr>
<tr>
<td>AHFS class</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>7811 (5.2)</td>
</tr>
<tr>
<td>Central nervous systemb</td>
<td>38 370 (25.4)</td>
</tr>
<tr>
<td>Ear, nose, and throat</td>
<td>7552 (5.0)</td>
</tr>
<tr>
<td>Hormone and synthetics</td>
<td>20 589 (13.6)</td>
</tr>
<tr>
<td>Formulary restrictedc</td>
<td>5069 (3.4)</td>
</tr>
<tr>
<td>Anti-infective</td>
<td>15 719 (10.4)</td>
</tr>
<tr>
<td>Autonomicd</td>
<td>8087 (5.3)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>34 860 (23.0)</td>
</tr>
<tr>
<td>Otherd</td>
<td>13 248 (8.8)</td>
</tr>
</tbody>
</table>

Drug (n = 630)
- Before 1981: 292 (46.3)
- 1981-1995: 158 (25.1)
- 1996-2009: 180 (28.6)

Patient (n = 46 021)
- Age, y
  - 18-64: 29 712 (64.6)
  - ≥65: 16 309 (35.4)
  - Mean (SD) [range]: 58.2 (16.8) [18.5-101.0]
  - Median (IQR): 59.5 (47.5-70.5)
- Sex
  - Men: 18 039 (39.2)
  - Women: 27 982 (60.8)
- Charlson comorbidity indexd
  - 0: 34 618 (75.3)
  - ≥1: 11 383 (24.7)
- No. of drugs used
  - 1-2: 15 686 (34.1)
  - 3-4: 10 993 (23.9)
  - 5-7: 10 243 (22.3)
  - ≥8: 9099 (19.8)
- Continuity of caree
  - Mean (SD): 1.09 (0.64)
  - Median (IQR): 1.00 (0.88)

Abbreviations: AHFS, American Hospital Formulary Service; IQR, interquartile range.

a Unless otherwise indicated, data are expressed as number (percentage) of prescribed drugs. Percentages have been rounded and may not total 100.

b For example, includes antidepressants, antipsychotics, anticonvulsants, anxiolytics, and antimigraine medicines.

c Also known as conditional listing, used in relation to drug expenditure policy, whereby the prescribing physician needs to justify the clinical need before the costs of therapy will be covered.

d Includes drugs such as albuterol sulfate, terbutaline sulfate, and cyclobenzaprine hydrochloride.

e Includes antihistamines, blood thinners and anticoagulants, and antineoplastics.
f Ranges from 0 to 25; 1 or greater indicates increased risk for death.

g Defined as the ratio of the number of a patient’s visits to the primary care physician to the square root of the patient’s total number of outpatient visits calculated using the medical services claims.

Results

A total of 46 021 patients received 151 305 incident prescriptions from January 1, 2005, through December 30, 2009. Off-label use was reported in 17 847 prescriptions (11.8%); in 14 431 of these cases (80.9%), the off-label uses lacked strong scientific evidence (Table 1). Mean (SD) patient age was 58.2 (16.8) years. Patients were predominantly women (27 982 [60.8%]); 11 383 patients (24.7%) had a Charlson comorbidity index of 1 or greater, and 19 342 (42.0%) used more than 4 unique drugs during the study period. Of the 630 prescribed drugs, 292 (46.3%) had been approved for market before 1981, whereas 180 (28.6%) were approved after 1995. The mean (SD) COC index was 1.09 (0.64). The follow-up time for a prescription ranged from 1 day to almost 6 years (median, 386 days; mean, 530 days).

The distribution of off-label use (with and without strong scientific evidence) by American Hospital Formulary Service drug class is shown in eTable 2 in the Supplement. For the 38 370 CNS drugs found, off-label use and off-label use without scientific evidence were reported in 9814 of 38 370 prescribed drugs (25.6%) and 8157 prescribed drugs (21.3%), respectively. Among the CNS drugs, off-label use was highest for anticonvulsants (2158 [65.6%]), antipsychotics (669 [51.4%]), and antidepressants (3657 [33.5%]); off-label use without strong scientific evidence for these drugs was reported in 2116 (64.3%), 668 (51.3%), and 3063 (28.1%), respectively.

Physicians discontinued 3484 drug treatments owing to ADEs. Most ADEs (2456 [70.5%]) occurred in the first year of treatment and, among these, 1228 (50%) occurred in the first 3 months. eTable 3 in the Supplement shows selected drugs with high levels of off-label use and the proportion of drugs with discontinuation of use owing to ADEs. The overall incidence rate of ADEs for all drugs was 13.2 per 10 000 person-months. The ADE rate for on-label use was lower (12.5 per 10 000 person-months) than for off-label use (19.7 per 10 000 person-months), a 44% increase in the risk for ADEs with off-label use (adjusted HR [AHR], 1.44; 95% CI, 1.30-1.60) (Table 2 and Figure 2). When off-label use was stratified to off-label use with and without strong scientific evidence, the ADE rates were 13.2 and 21.7 per 10 000 person-months, respectively. Com-
pared with on-label use, the AHRs (95% CI) for off-label use with and without strong scientific evidence were 1.10 (0.88-1.38) and 1.54 (1.37-1.72), respectively (Table 2 and Figure 3). Proportionality assumptions for the HRs were not violated. The median time to discontinue drug use owing to an ADE was shorter for drugs used off-label (146 days) compared with those used on-label (179 days).

Anti-infectives had the highest ADE rate (66.2 per 10 000 person-months), more than a 6-fold increase in risk for ADEs compared with gastrointestinal tract drugs (AHR, 6.33; 95% CI, 4.58, 8.76). Central nervous system and cardiovascular drugs had ADE rates of 18.1 and 15.9 per 10 000 person-months, respectively. Drugs approved after 1995 had ADE rates that were 55% higher than drugs approved before 1981 (AHR, 1.55; 95% CI, 1.39-1.73), and the same is true for drugs approved from 1981 to 1995 (AHR, 1.62; 95% CI, 1.45-1.80) (Table 2). Dose-response relationships were identified between the number of drugs the patient used and the risk for ADEs, in which patients using 8 or more drugs had more than a 5-fold increased risk for ADEs compared with patients using 1 to 2 drugs (AHR, 5.29; 95% CI, 4.39-6.38). Patients 65 years and older exhibited an increased risk for ADEs in an adjusted analysis compared with younger cohorts; however, the increased risk did not persist after adjusting for the number of drugs and patients’ comorbidities. Women also had a higher risk for ADEs than men (14.3 vs 11.7 per 10 000 person-months, respectively; AHR, 1.17; 95% CI, 1.06-1.28). After adjusting for other patient characteristics, the patients with a Charlson comorbidity index of 1 or greater had a lower risk for ADEs compared with patients with an index of 0 (AHR, 0.89; 95% CI, 0.81-0.98). The COC index was an important determinant of ADE detection, with a 19% increase in ADE rate per 1-unit increase in the COC index (AHR, 1.19; 95% CI, 1.12-1.26) (Table 2). In a subanalysis, we fit a model to drugs predominantly used for chronic conditions (by removing the anti-infective group) and found a slight change in the AHR for off-label use without strong scientific evidence (1.58; 95% CI, 1.41-1.77). The ADEs related to the gastrointestinal tract, nervous, respiratory, and musculoskeletal system organ classes were docu-

### Table 2. Association of ADEs and Drug and Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of ADEs</th>
<th>Person-months, No. per 10 000</th>
<th>IR per 10 000 Person-months</th>
<th>HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Multivariate Adjusted&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>On-label use</td>
<td>2968</td>
<td>237.5</td>
<td>12.5</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Off-label use</td>
<td>516</td>
<td>26.2</td>
<td>19.7</td>
<td>1.48 (1.35-1.64)</td>
<td>1.44 (1.30-1.60)</td>
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<tr>
<td>With strong scientific evidence</td>
<td>81</td>
<td>6.1</td>
<td>13.2</td>
<td>1.04 (0.84-1.30)</td>
<td>1.10 (0.88-1.38)</td>
</tr>
<tr>
<td>Without strong scientific evidence</td>
<td>435</td>
<td>20.1</td>
<td>21.7</td>
<td>1.62 (1.45-1.80)</td>
<td>1.54 (1.37-1.72)</td>
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<td>AHFS class</td>
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<tr>
<td>Gastrointestinal tract</td>
<td>98</td>
<td>16.0</td>
<td>6.1</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
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<tr>
<td>Central nervous system&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1096</td>
<td>60.7</td>
<td>18.1</td>
<td>2.82 (2.27-3.49)</td>
<td>3.06 (2.46-3.79)</td>
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<td>Ear, nose, and throat</td>
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<td>11.6</td>
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<td>0.44 (0.29-0.69)</td>
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<td>Hormone and synthetics</td>
<td>548</td>
<td>43.2</td>
<td>12.7</td>
<td>2.06 (1.64-2.59)</td>
<td>2.62 (2.09-3.29)</td>
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<tr>
<td>Formulary restricted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>114</td>
<td>11.8</td>
<td>9.7</td>
<td>1.66 (1.26-2.19)</td>
<td>1.89 (1.43-2.49)</td>
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<tr>
<td>Anti-infectives</td>
<td>80</td>
<td>1.2</td>
<td>66.2</td>
<td>5.63 (4.10-7.75)</td>
<td>6.33 (4.58-8.76)</td>
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<tr>
<td>Autonomic&lt;sup&gt;e&lt;/sup&gt;</td>
<td>141</td>
<td>16.8</td>
<td>8.4</td>
<td>1.39 (0.95-2.02)</td>
<td>1.73 (1.17-2.55)</td>
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<td>Cardiovascular</td>
<td>1354</td>
<td>85.7</td>
<td>15.9</td>
<td>2.73 (2.21-3.37)</td>
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<tr>
<td>Other&lt;sup&gt;f&lt;/sup&gt;</td>
<td>21</td>
<td>16.7</td>
<td>1.3</td>
<td>0.18 (0.11-0.29)</td>
<td>0.23 (0.14-0.38)</td>
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<tr>
<td>Drug age</td>
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<tr>
<td>Before 1981</td>
<td>754</td>
<td>75.3</td>
<td>10.0</td>
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<td>1981-1995</td>
<td>1140</td>
<td>79.1</td>
<td>14.4</td>
<td>1.49 (1.34-1.64)</td>
<td>1.62 (1.45-1.80)</td>
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<td>1996-2009</td>
<td>1590</td>
<td>109.3</td>
<td>14.5</td>
<td>1.49 (1.35-1.65)</td>
<td>1.55 (1.39-1.73)</td>
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<td>Patient age, y</td>
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<td>18-64</td>
<td>2079</td>
<td>162.2</td>
<td>12.8</td>
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<td>1 [Reference]</td>
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<td>≥65</td>
<td>1405</td>
<td>101.6</td>
<td>13.8</td>
<td>1.16 (1.07-1.27)</td>
<td>0.98 (0.90-1.07)</td>
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<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>1251</td>
<td>107.0</td>
<td>11.7</td>
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<tr>
<td>Women</td>
<td>2233</td>
<td>156.7</td>
<td>14.3</td>
<td>1.19 (1.09-1.30)</td>
<td>1.17 (1.06-1.28)</td>
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<td>Charlson comorbidity index&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>185.3</td>
<td>12.9</td>
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<td>≥1</td>
<td>1111</td>
<td>78.4</td>
<td>14.1</td>
<td>1.11 (1.02-1.22)</td>
<td>0.89 (0.81-0.98)</td>
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<tr>
<td>No. of drugs used</td>
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<td>29.4</td>
<td>4.4</td>
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<td>3-4</td>
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<td>50.3</td>
<td>7.5</td>
<td>1.86 (1.52-2.28)</td>
<td>1.90 (1.55-2.33)</td>
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<td>5-7</td>
<td>899</td>
<td>74.4</td>
<td>12.1</td>
<td>3.10 (2.56-3.76)</td>
<td>3.23 (2.66-3.92)</td>
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<tr>
<td>≥8</td>
<td>2079</td>
<td>109.6</td>
<td>19.0</td>
<td>4.93 (4.10-5.94)</td>
<td>5.29 (4.39-6.38)</td>
</tr>
<tr>
<td>COC index, mean (SD)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1.09</td>
<td>0.64</td>
<td></td>
<td>1.22 (1.16-1.30)</td>
<td>1.19 (1.12-1.26)</td>
</tr>
</tbody>
</table>

Abbreviations: ADE, adverse drug event; AHFS, American Hospital Formulary Service; COC, continuity of care; HR, hazard ratio; IR, incidence rate.

<sup>a</sup> Calculated using a marginal Cox proportional hazards regression model with a robust sandwich covariance estimator to account for intraclass correlation.

<sup>b</sup> Results from 2 multivariate analyses are included. The HR estimates for the other covariates when off-label use was divided according to scientific evidence were not shown here because the difference was not substantial.

<sup>c</sup> Includes antidepressants, antipsychotics, anticonvulsants, anxiolytics, and antimigraine medicines.

<sup>d</sup> Also known as conditional listing, used in relation to drug expenditure policy, whereby the prescribing physician needs to justify the clinical need before the costs of therapy will be covered.

<sup>e</sup> Includes drugs such as albuterol sulfate, terbutaline sulfate, and cyclobenzaprine hydrochloride.

<sup>f</sup> Includes antihistamines, blood thinners and anticoagulants, and antineoplastics.

<sup>g</sup> Ranges from 0 to 25; 1 or greater indicates increased risk for death.

<sup>h</sup> Defined as the ratio of the number of a patient’s visits to the primary care physician to the square root of a patient’s total number of outpatient visits calculated using the medical services claims. The HRs are calculated per 1 unit.

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<sup>1</sup> Defined as the ratio of the number of a patient’s visits to the primary care physician to the square root of a patient’s total number of outpatient visits calculated using the medical services claims. The HRs are calculated per 1 unit.
ment the most frequently (eTable 4 in the Supplement). Selected examples of ADEs associated with the most frequently used off-label drugs include akathisia resulting from the use of gabapentin for neuropenic pain; agitation associated with the use of amitriptyline hydrochloride for migraine; hallucinations with the use of trazodone hydrochloride for insomnia; QT interval prolongation with the use of quetiapine fumarate for depression; and weight gain with the use of olanzapine for depression.

Discussion

This study is, to our knowledge, the first to systematically evaluate the association between off-label use of drugs and the risk for ADEs in an adult population. The study is also the first to use electronically documented treatment indications and treatment outcomes to measure off-label drug use and ADE occurrence. We found that off-label use of drugs was associated with ADEs after adjusting for important patient and drug characteristics. Moreover, we noted a risk gradient with higher rates of ADEs for off-label uses lacking strong scientific evidence.

Although the intrinsic nature of the drug to cause ADEs is the same for on-label and off-label uses, it may be modified by a number of factors, including the off-label disease condition. In addition, the lack of approval from a regulatory body implies a lack of safe dose ranges and inadequate information on contraindications, which in aggregate make ADEs more likely. We found that 4 in 5 off-label prescriptions lacked strong scientific evidence, and this group had higher rates of ADEs. Off-label use may be clinically appropriate given the complexity of the patient's condition, the lack of alternative effective drugs, or after exhausting approved drugs. However, a lack of physician knowledge of approved treatment indications was shown to be a factor for off-label prescribing. Physicians are finding it difficult to keep up with rapidly changing medication information, and this lack of knowledge is affecting treatment of patients. Studies have shown that the number of drugs used by a patient strongly influences the risk for ADEs owing to an increased risk for inappropriate prescribing, drug-drug interaction, and drug-disease interaction. Similarly to other studies, we found the rates of ADEs were significantly higher among patients using drugs from the anti-infective, cardiovascular, and CNS drug classes. We also found the same age effect that was reported from the French pharmacovigilance study with the oldest group having a higher crude incidence rate of ADEs; however, after adjusting for the number of drug treatments, the effect disappears. Overall, this finding shows that the number of prescribed drugs is the strongest risk factor for ADEs. In our study, a higher risk for ADEs was observed for women, even after accounting for the COC index to mitigate the effect of high consultation rates among women. We also identified patients with a higher COC index as having a high risk for ADEs, possibly owing to surveillance detection biases with more opportunity to identify ADEs in their earlier stages.

Using appropriately configured computerized decision support systems, we could fill the knowledge gap in off-label prescribing by supplying clinicians with information on drug approval status and the degree of scientific evidence at the point of care. In addition, the inclusion of treatment indication in the electronic prescription would facilitate communication among physicians, pharmacists, and patients and may decrease medication errors (eg, wrong-patient errors and look-alike and sound-alike drugs). At the same time, these technologies could allow physicians to participate actively in the systematic collection of data to evaluate the benefits and risks associated with the off-label use of drugs. Moreover, monitoring patients in the community with a nurse or an interactive voice response system to detect drug-related problems and relaying this information to a community pharmacist or the treating physician would be one option of detecting and ameliorating these risks.

The study has several limitations. First, ADE identification depends on physicians and patients. Physicians are known to miss medication-related symptoms, and patients may not inform their physicians about all of their symptoms. Second, ADEs among patients with comorbidities may not be as easily attributed to the drug (vs the concurrent disease) and may not be identified. Third, patients with severe ADEs may visit hospitals and other physicians, and the ADEs might not be recorded in their EHR. All these limitations might have resulted in an underestimation of ADE incidence. However, the underestimation of ADE rates will likely affect on-label and off-label uses equivalently and thus not bias the association between drug approval status and ADEs. Although the ADEs were severe enough to warrant discontinuation of drug use, the ADEs were not documented with a severity scale, which limited subgroup analysis.

When classifying off-label use, we only considered the drug and the treatment indication. Our off-label definition did not consider the dosage, frequency, route of administration, duration of treatment, and patients' age range. A wider definition of off-label use could have increased the prevalence of off-label use.

In recent years, drug regulatory bodies have created mechanisms to expedite the drug review process and to give the public rapid access to drugs. In addition, they have mandated the life-cycle approach to drug evaluation with ongoing pharmacovigilance and risk evaluation and mitigation strategies. For example, France has passed a law to monitor off-label drug use and study the benefit-risk ratios of these uses in collaboration with the pharmaceutical industry. In this study, we demonstrated that an EHR system tailored to document treatment indications and the reason for treatment discontinuation can be used to monitor off-label drug use and its outcomes. Such a system can help to tackle fundamental problems in postmarketing surveillance of drugs, namely, the lack of an explicit link between prescribed drugs and their indication for use and the underreporting of ADEs. Large-scale documentation of drug indications, ADEs, and clinical variables within the EHR can facilitate powerful observational studies, comparative safety and effectiveness trials, and decision support systems. Moreover, linking a prescribed drug with an indication and outcome (eg, ADE) could be a meaningful-use objective, thereby advancing meaningful use to meaningful benefit.
In our study, the cost of ADEs was not measured. However, the cost can be estimated using previously published figures. Adverse effects that occur in nonhospital settings may lead to emergency department visits and hospital admissions. The mean cost of an emergency department visit without hospital admission has been estimated to range from $549 to $704 per ADE, whereas the estimated mean cost of treating an ADE resulting in hospital admission has been estimated to range from $5118 to $11,789 (in 2014 US currency). The median prevalence rate of hospitalizations resulting from ADEs has been estimated at 4.6%. The present study found 3484 ADEs in 46,021 patients; thus, the mean cost per ADE would range from $759 to $1214. Likewise, the mean cost per study patient would be $51 to $77.

Conclusions
Off-label drug use, and particularly off-label use without strong scientific evidence, is a risk factor for ADEs. Hence, physicians and physician organizations should recognize...
the enormity of the problem and be active participants in the promotion of cautious prescribing of drugs for off-label uses lacking strong scientific evidence. Future EHRs should be designed to enable postmarketing surveillance of treatment indications and treatment outcomes to monitor the safety of on- and off-label uses of drugs.

**ARTICLE INFORMATION**

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Author Affiliations: Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada (Eguale, Buckridge, Verma, Benedetti, Hanley, Tamblyn); Department of Medicine, McGill University, Montreal, Quebec, Canada (Eguale, Buckridge, Winslade, Tamblyn); Division of General Medicine and Primary Care, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts (Eguale); Department of Social and Administrative Pharmacy, School of Pharmacy, MCPHS University, Boston, Massachusetts (Eguale); Department of Mathematics and Statistics, McGill University, Montreal, Quebec, Canada (Hanley).

Author Contributions: Drs Eguale and Tamblyn had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Eguale, Buckridge, Verma, Winslade, Hanley, Tamblyn.

Acquisition, analysis, or interpretation of data: Eguale, Buckridge, Verma, Benedetti, Hanley, Tamblyn.

Drafting of the manuscript: Eguale, Verma, Hanley, Tamblyn.

Critical review of the manuscript for important intellectual content: Eguale, Buckridge, Verma, Winslade, Benedetti, Tamblyn.

Statistical analysis: Eguale, Buckridge, Verma, Benedetti, Hanley.

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Study supervision: Buckridge, Tamblyn.

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**REFERENCES**


Yelling “Fire!” in a crowded theater without any imminent danger is an oft-cited example of free speech that is not protected. For many years, the US Food and Drug Administration (FDA) has prohibited the promotion of unapproved uses of drugs. This restriction has recently been challenged under the guise of free speech. In a potential landmark decision in August 2015, a federal judge ruled against the FDA’s restrictions on off-label drug promotion, referencing protection by the First Amendment. Critics of off-label drug promotion point to dietary supplements as an example of the kinds of claims that are commonplace when regulation is lax and worry about an erosion of the authority of the FDA to ensure safety and efficacy of drugs. Are these concerns about safety warranted? Does evidence show that off-label prescribing might be less safe than on-label prescribing? In light of these concerns, the study of off-label drug use and adverse drug events by Eguale and colleagues in this issue of JAMA Internal Medicine is particularly timely.

The FDA has substantial responsibility and authority in the preapproval process of new drugs to ensure safety, efficacy, and accuracy in the approved label. The postapproval period is far less regulated. Although the FDA is clearly interested in postapproval drug safety and occasionally provides approval contingent on performance of additional studies, once a drug reaches the market, literally millions of patients may be exposed to that drug with limited ability to track its safety or effectiveness. Physicians are not legally required to follow the approved labeled indications, and the FDA even recognizes that off-label use of drugs may constitute good medical practice in some cases.

Of course, many examples of appropriate off-label uses of medications exist, and in some situations, off-label use of a drug may be the standard of care. Digoxin is approved for rate control in atrial fibrillation, whereas use of metoprolol is off-label. However, metoprolol, but not digoxin, is first-line therapy for rate control in evidence-based clinical guidelines. Moreover, off-label use may precede approval for an indication. Thalidomide was approved to treat leprosy in 1999. In 1999, it was reported to be effective for multiple myeloma; by 2003, the manufacturer of thalidomide reported that 92% of its sales came from the off-label use. Eventually in 2006, the multiple myeloma indication was added to the label.

Because physicians are not required to document intended indications, tracking off-label drug use is challenging. By all accounts, off-label prescribing is common. Among office-based physicians in 2001, an estimated 21% of overall prescriptions were off-label. Off-label use of cardiac medications and anticonvulsants was especially common, and the investigators reported that almost three-quarters of all off-label use had little or no scientific evidence to support the indication. Perhaps contributing to off-label use of drugs is a general lack of physician knowledge of FDA indications, with the frequent assumption of FDA approval for off-label indications with uncertain or absent evidence of benefit.

Although evidence of overall safety of off-label prescribing is limited, many individual reports of patient harm exist. A Knight Ridder investigative news series in 2003 alleged that off-label prescribing was routine and resulted in death or serious injuries to many patients. The report documented examples of adverse outcomes associated with off-label use of antipsychotics to treat behavioral issues in elderly patients with dementia, anticonvulsants to treat bipolar disorder, terbutaline for premature labor, and fluoxetine hydrochloride for pain. Other common off-label uses can have less serious but undesirable outcomes. For example, sleeping pills, approved only for short-term management of insomnia, are prescribed long term, leading to tolerance. Stimulants, such as modafinil, are used to