Antidepressant use in the United States has increased over the last 2 decades. A suspected reason for this trend is that primary care physicians are increasingly prescribing antidepressants for nondepressive indications, including unapproved (off-label) indications that have not been evaluated by regulatory agencies. However, the frequency with which physicians prescribe antidepressants for nondepressive indications is unknown because treatment indications are rarely documented. We analyzed the prevalence of treatment indications for antidepressants and assessed temporal trends in antidepressant prescribing for depression.

Methods | This study used data from the Medical Office of the 21st Century (MOXXI) research platform. MOXXI is an electronic medical record (EMR) and prescribing system that has been used by primary care physicians in community-based, fee-for-service practices around 2 major urban centers in Quebec, Canada. During the study period, approximately 185 physicians (25% of eligible) and 100,000 patients (30% of all who visited a MOXXI physician) gave informed consent to use the EMR and have their information used for research purposes.

### Table. Treatment Indications and Off-Label Prescribing for Antidepressant Prescriptions in Quebec, Canada, 2006-2015

<table>
<thead>
<tr>
<th>Treatment Indication</th>
<th>No. of Prescriptions (%)</th>
<th>No. of Prescriptions by Pharmacological Class (%)</th>
<th>No. of Off-Label Prescriptions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive disorders</td>
<td>56 154 (55.2)</td>
<td>26 339 (46.9)</td>
<td>15 259 (27.2)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>18 849 (18.5)</td>
<td>12 466 (66.1)</td>
<td>5076 (26.9)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10 347 (10.2)</td>
<td>19 (0.2)</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Pain</td>
<td>6241 (6.1)</td>
<td>24 (0.4)</td>
<td>1340 (21.5)</td>
</tr>
<tr>
<td>Panic disorders with or without agoraphobia</td>
<td>4174 (4.1)</td>
<td>3280 (78.6)</td>
<td>751 (18.0)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1550 (1.5)</td>
<td>63 (4.1)</td>
<td>958 (61.8)</td>
</tr>
<tr>
<td>Migraine</td>
<td>1498 (1.5)</td>
<td>6 (0.4)</td>
<td>22 (1.5)</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>1111 (1.1)</td>
<td>875 (78.8)</td>
<td>177 (15.9)</td>
</tr>
<tr>
<td>Vasomotor symptoms of menopause</td>
<td>856 (0.8)</td>
<td>112 (13.1)</td>
<td>736 (86.0)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>568 (0.6)</td>
<td>434 (76.4)</td>
<td>134 (23.6)</td>
</tr>
<tr>
<td>Nicotine dependence</td>
<td>514 (0.5)</td>
<td>6 (0.1)</td>
<td>514 (100.0)</td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder</td>
<td>389 (0.4)</td>
<td>16 (4.1)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>263 (0.3)</td>
<td>211 (80.2)</td>
<td>35 (13.3)</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>261 (0.3)</td>
<td>39 (14.9)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Premenstrual disorders and syndromes</td>
<td>212 (0.2)</td>
<td>193 (91.0)</td>
<td>17 (8.0)</td>
</tr>
<tr>
<td>Digestive system disorders</td>
<td>119 (0.1)</td>
<td>4 (3.4)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Urinary system disorders</td>
<td>109 (0.1)</td>
<td>0 (0.0)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>76 (0.1)</td>
<td>54 (71.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>317 (0.3)</td>
<td>61 (19.2)</td>
<td>11 (3.5)</td>
</tr>
<tr>
<td>Any indication</td>
<td>101 759 (100.0)</td>
<td>43 462 (42.7)</td>
<td>23 898 (23.5)</td>
</tr>
</tbody>
</table>

Abbreviations: SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

* Among all antidepressant prescriptions, 1.8% had multiple treatment indications recorded and were assigned to multiple categories. As a result, the sum of prescriptions across the individual treatment indication categories exceeds the number of prescriptions for any indication (last row).

* Percentages were calculated using the total number of antidepressant prescriptions for any indication (N = 101 793) as the denominator.

* Percentages for each pharmacological class were calculated using the total number of prescriptions for the indication as the denominator.

* Includes desvenlafaxine, duloxetine, and venlafaxine.

* Includes amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, and trimipramine.

* Includes bupropion, maprotiline, mirtazapine, trazodone, and vortioxetine.

* For each treatment indication category, a prescription was classified as off-label if the drug was not approved for the indication by Health Canada or the US Food and Drug Administration as of September 2015. For any indication (last row), a prescription was classified as off-label if the drug was not approved for all of its recorded indications. Percentages were calculated using the total number of prescriptions for the indication as the denominator.

* Includes anxiety, generalized anxiety disorder, and other anxiety disorders except panic disorders and phobias.
Compared with nonconsenters, MOXXI physicians were younger and MOXXI patients were older with more health complexities.4

This study included all prescriptions written for adults between January 1, 2006, and September 30, 2015, for all antidepressants except monoamine oxidase inhibitors. Physicians had to document at least 1 treatment indication per prescription using a drop-down menu containing a list of indications or by typing the indication(s). In a validation study, these indications had excellent sensitivity (98.5%) and high positive predictive value (97.0%).5 Prescriptions were classified as on-label or off-label depending on whether the drug was approved for the indication by Health Canada or the US Food and Drug Administration by September 2015. Temporal trends in antidepressant prescribing for depression were measured using generalized linear risk difference models for binary outcomes, with an identity link. A linear effect of calendar time (in years) was modeled on the probability of antidepressant prescribing for depression, adjusted for patient age and sex and accounting for multilevel clustering of prescriptions using an alternating logistic regression algorithm.6 All statistical analyses were conducted using SAS (SAS Institute) software, version 9.4. This study was approved by the McGill institutional review board.

Results | During the study period, 101 759 antidepressant prescriptions (5.9% of all prescriptions) were written by 158 physicians for 19 734 patients. Only 55.2% of antidepressant prescriptions were indicated for depression. Physicians also prescribed antidepressants for anxiety disorders (18.5%), insomnia (10.2%), pain (6.1%) and panic disorders (4.1%) (Table). For these indications, respectively, the most frequently prescribed antidepressants were citalopram (29.5% of prescriptions for the indication), trazodone (76.6%), amitriptyline (65.1%), and paroxetine (35.9%).

For 29.4% of all antidepressant prescriptions (65.6% of prescriptions not for depression), physicians prescribed a drug for an off-label indication, especially insomnia and pain. Physicians also prescribed antidepressants for several indications that were off-label for all antidepressants, including migraine, vasomotor symptoms of menopause, attention-deficit/hyperactivity disorder, and digestive system disorders (Table).

Between 2006 and 2015, the percentage of antidepressants prescribed for depression decreased significantly, with an adjusted 5-year risk difference of −9.73% (95% CI, −11.86% to −7.61%) for serotonin-norepinephrine reuptake inhibitors, −3.96% (95% CI, −5.33% to −2.59%) for selective serotonin reuptake inhibitors, and −2.99% (95% CI, −4.90% to −1.08%) for tricyclic antidepressants (Figure). However, the percentage of other antidepressants (especially mirtazapine) prescribed for depression increased significantly, with an adjusted 5-year risk difference of 2.36% (95% CI, 0.32% to 4.40%).

Discussion | Between 2006 and 2015, primary care physicians in Quebec commonly and increasingly prescribed antidepressants for nondepressive indications. When physicians prescribed antidepressants for insomnia and pain, they often prescribed antidepressants off-label.

Figure. Percentage of Antidepressant Prescriptions for Depression by Pharmaceutical Class, 2006–2015

The study was limited by a selective patient population and a small number of prescribers from 1 Canadian province. However, this is the first study to our knowledge to describe the prevalence of treatment indications for antidepressants using validated, physician-documented treatment indications recorded at the point of prescribing. The findings indicate that the mere presence of an antidepressant prescription is a poor proxy for depression treatment, and they highlight the need to evaluate the evidence supporting off-label antidepressant use.

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COMMENT & RESPONSE

Risk of Anaphylaxis With Intravenous Iron Products

To the Editor The study by Dr Wang and colleagues1 reported the risk of anaphylaxis with different intravenous iron products. I have several concerns.

One concern is the definition of anaphylaxis. In the article’s online Supplement, both anaphylaxis criteria B and C include “injection of diphenhydramine.” Given that diphenhydramine is used as premedication prior to intravenous iron, a significant majority of the reactions ostensibly attributed to the iron were due to diphenhydramine.2 In the Methods section, the authors noted that minor self-limited reactions such as minor allergic reactions would be wrongly labeled as anaphylaxis events. It would be informative to know the rates of anaphylactic reactions when patients who received diphenhydramine were excluded.

A second concern is that these data need to be put into perspective by comparing intravenous iron products with other commonly used drugs. For example, anaphylaxis to penicillin is reported in 10 to 50 per 100 000 treatment courses with a fatality rate of 1 to 2 per 100 000 courses, which is in the same range as that reported for intravenous iron.3

Third, death rates, which were reported in the article’s online Supplement, were not discussed in the article. Reviewing data from eTables 3 and 4, it appears that death rates for all iron products were very similar, suggesting that safety rates are likely to be similar for all products and that the anaphylaxis rates for iron dextran may have been overestimated. Is it possible that criteria by which anaphylaxis was defined differed for different products?

Finally, it should be emphasized that the study population, with an average age of 73 to 74 years, was not representative of many patients receiving intravenous iron, including patients who have inflammatory bowel disease or heavy uterine bleeding, are pregnant, or are undergoing bariatric surgery. It is important not to extrapolate rates from older adults to these younger (and potentially healthier) individuals.

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In Reply In response to Dr DeLoughery’s concern about diphenhydramine, provided is a sensitivity analysis that excluded all anaphylaxis cases with the claim of “injection of diphenhydramine” (Table I). Results are consistent with the primary analysis.

Regarding incidence rates, as discussed in our article, rates from our study were substantially lower than those reported from clinical trials of intravenous iron products. Although other study populations might have contributed to the observed differences, other differences in identifying and reporting anaphylaxis cases during clinical trials and during general clinical practice might also be relevant. Practicing physicians might not classify less severe or atypical anaphy-