Vanessa Young of Oakville, Ontario died suddenly on March 19, 2000 at age 15. She was taking cisapride, a drug prescribed to “enhance stomach emptying” of whose link to fatal cardiac dysrhythmias the US FDA warned American doctors two months earlier. Health Canada delayed its own alert until after Vanessa’s sudden cardiac arrest at home.1 Her father Terence Young became the Conservative MP for Oakville, Ontario and campaigned relentlessly for improved drug safety. In December 2019 the Protecting Canadians from Unsafe Drugs Act came fully into force. Vanessa’s Law requires hospitals to report serious adverse drug reactions and medical device incidents to Health Canada.2

Because signals of serious harms often surface years after drugs are licensed, regulatory agencies issue drug safety advisories intended to warn and update prescribers and patients. How consistent are such warnings around the world?

An international team including the Therapeutics Initiative examined drug safety advisories issued during 2007-2016 by Health Canada (HC), the UK Medicines and Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMA), the Australian Therapeutics Goods Administration (TGA) and the US Food and Drug Administration (FDA). We found that warnings differ significantly in frequency, approach and content,3,4 reflecting differences in legislated authority, agency capabilities, and transparency. Safety alert wording also reflects the level of pharmaceutical industry involvement.5 Prescribers and patients in one country may be alerted sooner than their counterparts elsewhere.

Health Canada’s approach

Health Canada (HC) regulates product monographs, showing indications and contraindications, warnings, precautions, adverse reactions, and potential drug interactions. They are located easily by a simple online search, or from Health Canada’s Drug Product Database.6 Producing the monograph is part of the drug approval process. Product monographs sometimes provide data about drug harms that are not published elsewhere. Tables summarizing adverse events observed in clinical trials can be more informative and much easier to access than journal articles.

When a new signal of serious harm is detected, HC often distributes a safety advisory and updates the monograph simultaneously. Advisories are posted at HC’s website and are sent to individual clinicians as a ‘Direct Health Professional Communication’. A recent example is HC’s October 30, 2020 update to safety labelling for benzodiazepines and “Z-drugs”.7 This alert emphasizes risks of problematic use and substance use disorder, severe withdrawal symptoms, falls and fractures, and accidental death when combined with opioids.

International Experience with Drug Safety Advisories

Analysis of 1,441 regulatory drug safety advisories issued over a 10-year period (pertaining to 680 drug safety concerns) found that only 10% were issued by all regulators where the drug was approved.8 Health Canada issued warnings for only half of the drug safety issues identified by regulators in the UK, Australia, and the United States. The following examples show how timeliness and strength of safety advisories vary.

Cardiac dysrhythmias

Regulatory alerts about serious drug harms could potentially save lives. During 2010-2016, Canadian, Australian, UK and US regulators issued 164 safety advisories about cardiac harms, of which 59% concern dysrhythmias. Of 61 drugs involved, only 9 attracted warnings in all four countries.9 Citalopram and escitalopram were subjects of 7 advisories during 2011-2012. The 4 regulators offered similar information about QT prolongation...
and advised against high doses. Only the FDA and Health Canada mentioned a risk of death. Advice on ECG monitoring also differed. The MHRA advised only performing ECGs in patients with cardiac disease before initiating treatment, and in patients with cardiovascular symptoms. Other regulators advised “more frequent” ECG monitoring in patients at risk of QT prolongation, without specifying frequency.

**Direct oral anticoagulants (DOACs)**

Australia approved dabigatran after the US and Canada, but in 2010 it was first to warn of risks of hemorrhage. The FDA and Health Canada approved dabigatran in 2008, but the FDA’s bleeding warning was not issued until 2013, and Health Canada’s not until early 2015. To date, the Australian TGA is the sole regulator to issue an advisory on bleeding risks of rivaroxaban.10 DOACs were responsible for many spontaneous reports to the FDA Adverse Event Reporting System. This drug class exemplifies how the approach of Canadian, UK, Australian and US regulators differed.3 Between 2007 and 2016, regulators issued 19 advisories on risks of bleeding for dabigatran, apixaban and rivaroxaban, including 3 warnings about interactions between dabigatran and antiarrhythmic drugs. Of 19 alerts, Health Canada issued 2, the MHRA 8, the TGA 5, and the FDA 4. Inconsistent approaches for different DOACs may have led to misconceptions about the relative safety of one drug or another within the class.3

**Fluoroquinolone antibiotics**

Between 2007 and 2016, regulators issued 9 advisories about this antibiotic class: Canada 4, Australia 1 and the US 4. Eight addressed specific fluoroquinolones regarding dysglycemia and liver disorders (levofloxacin), hepatotoxicity and serious skin reactions (moxifloxacin) and worsening symptoms in myasthenia gravis (moxifloxacin, ciprofloxacin, levofloxacin). Class-related advisories warned about tendon rupture, retinal detachment, aortic aneurysms, peripheral neuropathy, worsening myasthenia symptoms or altered blood glucose regulation.

**Are drug advisories relevant or important?**

Starting in 1998, the TI concluded that levofloxacin was not superior to other antibiotics for its approved indications,11 and that gatifloxacin and moxifloxacin “typically provide no therapeutic advantage over other antibiotics for most community-acquired infections”.12 We found no evidence favouring levofloxacin or moxifloxacin for acute bacterial sinusitis, community acquired pneumonia or acute exacerbations of chronic bronchitis.13-17 In 2008 Australia’s TGA warned that fluoroquinolone antibiotics were associated with tendon disorders, and the UK warned that moxifloxacin could cause life-threatening liver injury. **Canadian doctors did not receive a liver injury warning until 2010.** After a 2018 review of adverse drug reactions, the European Pharmacovigilance Committee (PRAC) recommended that fluoroquinolones be prescribed only as a last resort for acute cystitis, acute exacerbations of chronic obstructive pulmonary disease, acute bacterial sinusitis, and acute otitis media.18 An October 29, 2020 EMA alert warns of an association of recent fluoroquinolone use with mitral and aortic regurgitation.19 We still prescribe too many fluoroquinolone antibiotics.

**Global coordination in the international response to Covid-19** shows the potential to coordinate responses to health emergencies. Like viruses, drug safety concerns transcend borders. Consistent and coordinated pan-jurisdictional drug safety advice to prescribers and citizens could be more effective than current approaches.

**Conclusions**

- Better awareness of drug safety advisories from their own and other countries could help prescribers and patients seek the safest available drugs.
- When drug safety warnings differ, clinicians and the public need to know why. Regulators should provide the underlying rationale and an international context when issuing new drug safety warnings.

![These searchable sites provide drug safety advisories from the respective jurisdictions](image)

<table>
<thead>
<tr>
<th>Canada</th>
<th>Health Canada</th>
<th>Advisories, Warnings and Recalls</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>FDA</td>
<td>Recalls, Market Withdrawals and Safety Alerts</td>
</tr>
<tr>
<td>UK</td>
<td>MHRA</td>
<td>Drug Safety Update</td>
</tr>
<tr>
<td>Australia</td>
<td>TGA</td>
<td>Safety Alerts</td>
</tr>
</tbody>
</table>

In 2021 the Therapeutics Initiative website will offer a search engine for international drug safety advisories. Please subscribe to our email notification service to be notified when this new search engine becomes available.

**SUBSCRIBE:** [https://ti.ubc.ca/subscribe](https://ti.ubc.ca/subscribe)

For the complete list of references go to: [https://ti.ubc.ca/letter128](https://ti.ubc.ca/letter128)
References


