Drug safety without borders: concerns about bupropion

In the current regulatory system, advisories on drug safety stop at national borders, and information about international postmarketing experience is difficult to obtain. Is a death or a serious adverse event in one country of no interest to those who take the same drug for the same indication in another country? The recent experience with bupropion highlights the need for an international approach to drug safety monitoring and reporting.

Bupropion was licensed in Canada in 1998 for the treatment of depression (Wellbutrin) and for smoking cessation (Zyban). It was licensed only for smoking cessation in the United Kingdom (UK) in June 2000 (Zyban). Bupropion has been the subject of safety advisories in both countries.[1-3]

More Canadians have been prescribed bupropion because it has been on the market longer and has 2 indications. However, physicians and health authorities in the UK have reported 2 times more adverse drug reactions, 11 times more deaths and 3.8 times more seizures per 1000 prescriptions than in Canada (Table 1). Canadian reporting rates also lag for depression and smoking cessation.

The UK devotes more resources to postmarketing surveillance than Canada, including adverse event monitoring and the use of a visual symbol, the black triangle, on the product monograph when a drug is under intense surveillance.[4] Nonetheless, underreporting seems likely in both countries; the reported seizure rate in the UK was only 34% of the rate reported by the manufacturer in premarketing trials.[3]

Ample evidence exists for widespread underreporting of adverse drug reactions.[5-7] The usual estimate is that less than 10% of adverse drug reactions are reported. Our data suggest that 2 industrialized countries may have as much as a 25-fold difference in reporting rates. If the 10% rate applies to the UK, Canada would be missing 99.6% of adverse reactions and nearly 99% of deaths.

These findings reinforce the recent commentary in *CMAJ* that highlighted the inadequacy of drug safety monitoring and reporting in Canada.[8,9] Provision of international postmarketing information in safety advisories is no replacement for an adequately resourced postmarket surveillance system. However, it is an inexpensive step that could immediately help protect public safety.

Table 1: Reports of suspected adverse reactions to bupropion in Canada[1] and the United Kingdom[3]

	Canada		UK
Variable	All bupropion	Zyban	Zyban
Bupropion prescriptions	1 944 000	1 245 000	500 000
Prescriptions per 1000 population	62.54	40.06	8.37
Reports of adverse drug reactions	1127	NA	6975
Reports of adverse drug reactions per 1000 prescriptions	0.58	NA	13.95
Reports of serious adverse drug reactions	682	573	NA
Reported deaths	19	12	57
Reported deaths per 1000 prescriptions	0.01	0.01	0.11
Reported seizures	172	120	168
Reported seizures per 1000 prescriptions	0.09	0.10	0.34

Note: NA = not available.

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Caring for refugees

I read with interest the article by Erica Weir concerning caring for refugees in the Canadian context.[1] I would like to bring 2 small corrections to the attention of your readers.

The physicians who perform med-

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ical examinations for immigration applicants are authorized to undertake these services by Citizenship and Immigration Canada and do not work for Health Canada as indicated in the article. For reference, a listing of these physicians can be found at the department's Web site at www.cic.gc.ca /english/info/medical.html.

Second, the guidelines for the management of immigrants and refugees under surveillance for tuberculosis, noted in the article, have been revised since their initial publication in 1993. The latest guidelines in this regard were published in 2001[2] and are available on Health Canada's Web site at www.hc-sc.gc.ca/pphb-dgspsp/publicat/ccdr-rmt c/01vol27/dr2719ea.html.

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[The author responds:]

I thank Brian Gushulak for his attention to the column and for offering these corrections.

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Moxibustion

I was very surprised to see the article entitled "Unusual skin findings in a patient with liver disease."[1] The title implies that the skin manifestations described are due to liver disease and it also highlights that these findings are unusual.

Moxibustion has been used extensively in the Far East (Southeast Asia, China, India and Japan) for many centuries and for many kinds of diseases, including pleurisy, pneumonia, abdominal pain, chest pain and local pains, and is equivalent to the Western medicine practice of prescribing hot compresses as an anti-irritant to attract white blood cells and antibodies to the irritated area.

The term moxibustion refers to the application of a small amount of a dried plant material (*Artimisia moxa*), but it usually also involves scraping the skin with, traditionally, copper coins to create redness (see the right-hand figure in the *CMAJ* article). Glass cups are also used; these leave much larger marks than the ones shown in the left-hand figure (usually 2–3 cm in diameter). A drop of alcohol is placed in the cup, lit with a match and immediately applied to the painful area. Instantly, the flame goes out as the 20% oxygen is used up; the skin is sucked up into the cup and allowed to stay in place for a few minutes (creating a red area) and then pulled off. This process is sometimes associated with acupuncture.

I lived in China for 16 years and saw innumerable people with these skin manifestations.

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[The author responds:]

I am grateful to Dwight Peretz for his insights related to traditional Asian medical practices. I agree that moxibustion, coining, cupping and other traditional practices are extremely common, both in Asia and among immigrant populations in Canada. Nonetheless, the stigmata of these practices remain unfamiliar to many clinicians who have not had the benefit of practising in Asia or among Asian immigrant populations. Recognition of these clinical signs for what they are will allow clinicians to avoid misdiagnosis and may provide insights into the health beliefs of individual patients. I hope that the publication of the photographs in my article[1] has helped to familiarize clinicians with the skin manifestations of these traditional techniques.

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Debate over group B streptococcal recommendations

The Canadian Task Force on Preventive Health Care has made recommendations on 3 strategies to prevent group B streptococcal (GBS) infection in neonates.[1] The recommendations are not consistent with the information provided in the article and are at odds with the existing national guidelines.[2]

Strategy A is designed to screen all women at 35–37 weeks' gestation for GBS colonization and treat colonized women with risk factors. Strategy B is designed to screen all women and treat all who are colonized. And strategy C is designed to treat on the basis of risk factors alone. The task force's preferred strategy is strategy A. Strategy C is deemed to be the least favoured strategy because there is insufficient evidence to evaluate its effectiveness. However, strategy C would lead to treatment of the same group of infants as strategy A and those whose mothers have risk factors but have a negative screening result. This strategy would also result in treatment when the screen failed to identify colonization of the mother and when the mother was colonized after screening.

Women presenting in preterm labour will be largely unscreened be-