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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