CANADA'S ADVERSE DRUG REACTION REPORTING SYSTEM: A FAILING GRADE

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ABSTRACT

An article in the National Post on suicidal effects associated with varenicline (Champix) highlights deficiencies in the Canadian spontaneous reporting system (SRS) for adverse drug reactions (ADRs). The issues of under-reporting, poor quality information, duplication of reports and lack of a population denominator of drug use are discussed. Canada's SRS is deficient. There are immediate and medium-term actions that could be instituted that would improve pharmacovigilance in Canada. However, education about appropriate prescribing, the recognition of ADRs, and the duty to report them is a key long-term strategy to improving the pharmacovigilance system and should be included at every opportunity in the training of healthcare professionals so that life-long habits are developed. In addition to changes at Health Canada, greater emphasis needs to be placed on training in therapeutics, understanding drug safety, and the responsibility of healthcare providers in reporting risks in the curricula of medical and nursing schools.

In an article in the National Post, Culbert and Calman used adverse drug reaction (ADR) reports from the Canadian spontaneous reporting system (SRS) to examine suicidal effects associated with varenicline (Champix).[1] Their report highlights deficiencies in the SRS. What are the issues and how could the pharmacovigilance system be improved?

The worldwide foundation of drug safety monitoring for the past 50 years has been the SRS. In these systems, case reports of suspected ADRs are submitted to a national pharmacovigilance centre by healthcare providers, such as physicians, pharmacists and nurses, either directly or via the manufacturer of the drug. In some countries, including Canada, the national SRS provides an opportunity for direct reporting by patients.

In their early years, SRSs had some successes, especially in the United Kingdom, Sweden and the Netherlands due, in part, to innovative individuals in leadership positions in their regulatory agencies. The successes include the detection of the association between oral contraceptive usage and thromboembolic disease,[2-4] drug-induced blood disorders,[5,6] symptoms associated with triazolam,[7] and Guillain-Barré syndrome associated with zimeldine.[8] However, SRSs have also failed to identify many drug safety risks.

SRSs depend on patients reporting events that they experience during their use of a drug to healthcare professionals, who recognize that the event could be an ADR, find a reporting form, complete it, and submit it. This chain of events may never be started or, if it is, is easily broken and, consequently, under-reporting is a major problem with these systems. Less than 10% of ADRs, perhaps as few as 1-2%, are thought to be reported in SRSs. A review of 37 studies from 12 countries, including one from Canada, provided an estimated median rate of under-reporting of 94%.[9] In some situations, however, reporting is improved. These include when the ADR is life-threatening,[2] when a drug is new,[10] when a case report of the ADR has been published in a prominent medical journal or regulatory notice,[11,12] or when a drug safety issue has attracted mass media attention.

The reasons for under-reporting are numerous and complex.[13] They include the mistaken belief that only safe drugs are approved for marketing, ignorance of the reporting requirements, diffidence about reporting mere suspicions which might lead to ridicule, and fear of involvement in litigation.

Under-reporting is, however, only one limitation of SRSs. Another is the quality of the reports. The essential information on a suspected

ADR is the patient's age and gender, health problem treated by the suspected drug, treatment details including drug name, dose and dates, description of the reaction, all other drug information, and the eventual outcome.[14] In addition, it is preferable to have details of the patient's relevant medical history, the response to stopping the suspected drug and, if done, the response to restarting the drug. This is an extensive list for busy healthcare professionals to report and, consequently, it is likely that important information in ADR reports is often missing or inadequate.

In the 1990s, a study to evaluate the introduction of a program in which healthcare professionals were encouraged to report potential ADRs to regional centres in Canadian faculties of pharmacy provided an opportunity to assess the quality of ADR reporting.[15,16] Information from ADR reports submitted to Health Canada was compared with that from reports submitted to the Saskatchewan centre. Only 40% of the reports to Health Canada had sufficient information to assess the potential ADR as 'definite' or 'possible,' suggesting that reports to the SRS are often incomplete and of poor quality.

Reports submitted to any pharmaco-vigilance agency should be used to evaluate the potential causal relationship between drug exposure and an ADR. Methods used vary widely, but all depend upon ADR reports having sufficient and necessary detailed information. Too often the lack of data quality in reports leads to a non-specific causality assessment. An evaluation of reports submitted to an ADR monitoring program run by the Ontario Medical Association in the 1990s found that 86% of the cases were rated as having a 'possible' ADR, while only 13% were rated as 'probable' and 1% as 'doubtful.'[17] If the relationship between a drug and an ADR can only be assessed as 'possible,' it is neither strong enough to accept causality nor weak enough to reject it, which offers little guidance to healthcare providers and regulators and leads to ineffective pharmacovigilance.

Report duplication is another limitation that makes ADR information from the Canadian SRS difficult to use, as Culbert and Carman found.[1] The 53,109 ADR reports received by Health Canada in 2012 related to 36,101 individuals,[18] indicating that there are, on average, about 15 reports for every 10 patients. Duplication occurs when reports are received from multiple sources, e.g. the patient, different healthcare providers and the manufacturer, and when reporters submit more than once, e.g. an initial report and subsequent follow-ups. All reports for a patient should be aggregated, not left in the database separately. Multiple reports not only make working with the information difficult but potentially misleading.

A further problem with SRSs is that the total number of patients receiving a drug is unknown so that the rate of occurrence of an ADR cannot be directly estimated and only numbers of ADRs are reported. An article in the October 2004 issue of the Canadian Adverse Reaction Newsletter stated that, between January 2000 and May 2004, Health Canada had received 132 and 82 ADR reports of serious infection with infliximab and etanercept of which 14 and seven, respectively, had died.[19] Do these numbers imply that infliximab has a higher risk than etanercept? If the drugs are used at the same rate, the answer would be possibly, but if infliximab is used much more frequently than etanercept, the answer is likely to be no.

Culbert and Carman[1] reported that there were '129 reports of adverse reactions to Champix and 13 to Zyban in 2013,' which appears to make Champix look riskier than Zyban. However, they also noted that 625,000 prescriptions for Champix and 38,000 for Zyban were filled in 2013. Using these figures gives approximate rates of ADRs to Champix and Zyban of 1 in 5,000 and 1 in 3,000 prescriptions, respectively, which suggests a greater risk with Zyban than Champix.

In its report on infliximab and etanercept,[19] Health Canada emphasized that the SRS data cannot be used to determine the incidence of ADRs or to make quantitative drug safety comparisons between products because ADRs are under-reported. This argument should not be used as the reason for failing to estimate ADR rates using drug sales information. The under-reporting of ADRs certainly means that individual rates are under-estimates, but unless there is a reason to suspect wide variation in the degree of under-reporting for different drugs, any comparisons of the relative difference in ADR rates between drugs remain valid and much more useful for healthcare providers than mere ADR numbers.

These deficiencies in SRSs have led to

questioning of their continued usefulness,[20] but, there is no real alternative to SRSs that would begin to evaluate reports of suspected ADRs as soon as the marketing of a new drug commences. Therefore, SRSs are likely to remain in place as a front-line defence against previously unidentified ADRs. Nevertheless, this does not mean that they cannot be improved.

Regrettably, there appears to be little impetus to radically improve pharmacovigilance in Canada, despite the 59 recommendations made in 2001 by the coroner's jury following the well-publicized inquest into the death of Vanessa Young.[21] These recommendations included an arm's-length body independent from Health Canada dedicated to drug safety with mandated responsibilities to research drug safety, investigate ADRs and issue warnings to the public, healthcare providers and hospitals (a recommendation that has been repeated many times[22,23]), as well as mandatory reporting of all serious ADRs within 48 hours, promoting an international database of ADRs, and harmonizing drug information with other countries. Health Canada has instituted some improvements in the timeliness and clarity of communications about drugs and their risks,[24] increased its use of serious safety warnings to new drugs,[25] and now posts safety evaluations online.[26] The more innovative and expensive recommendations, however, remain unimplemented.

Mandatory ADR reporting by hospitals and other institutions has been promoted to reduce under-reporting and is included in new federal legislation enacted in 2014 (Vanessa's Law).[27] ADR reporting has been compulsory for pharmaceutical companies for many years. In countries where ADR reporting is mandatory, little improvement in the reporting rate has been seen. For example, in Sweden, where ADR reporting is mandatory, the under-reporting rate exceeded 85%.[28] Mandatory reporting also does not appear to provide better signals about ADRs than voluntary reporting.[29] Whether reporting is compulsory or not, if healthcare providers fail to recognize an ADR, they will not report it. They will also not report it if the process to do so is not integrated within the clinical documentation system.[30]

Establishing a separate drug safety organization or even one at arm's-length from Health Canada would be expensive. Since the directorate responsible for pharmacovigilance and other post-approval activities receives less than 25% of the regulatory agency's budget,[31] it seems obvious that Health Canada places a greater focus on pre-market evaluations. This conclusion is reinforced by the fact that Health Canada's support was always 'paltry'[29] for the regional ADR reporting centres in Canadian faculties of pharmacy.[15,16] If resources can be found for the Drug Safety and Effectiveness Network[32] whose effectiveness has recently been questioned,[33] why can they not be found for proactive pharmacovigilance that could actually minimize the number of patients impacted by safety risks that emerge as new drugs are integrated into clinical practice? Any new funding for pharmacovigilance in Canada should not be used for more of the same current activities but for innovative developments.

Some of these actions would cost relatively little. For example, prescribers and patients could be alerted to new products by the inclusion of a unique symbol in all material relating to drugs, such as the Compendium of Pharmaceuticals and Specialties and drug benefit lists. Healthcare providers in the United Kingdom have been alerted to new drugs by the use of an inverted black triangle in the British National Formulary and other informational documents for many years and, in 2013, the European Medicines Agency adopted the same system for the European Union.

Health Canada should also provide feedback to reporters of ADRs. To be impactful, feedback should be tailored into several formats,[34] such as an upgraded MedEffect Canada, manufacturers' literature, scientific publications, letters and other direct communications. Feedback must not merely consist of a printout of all similar ADR reports received by Health Canada about the drug because this would be more likely to deter healthcare professionals from reporting than encourage them.

Health Canada should also initiate proactive pharmacovigilance systems. The lack of a central organization processing prescriptions in Canada prevents the establishment of a system such as the United Kingdom's Prescription-Event Monitoring.[35] However, a similar method, known as the Pharmacy Medication Monitoring Program (PMMP), was established at McMaster University in the 1990s.[36]

Patients dispensed selected drugs were registered by pharmacists and later contacted by research staff by telephone so that a questionnaire about the patient's experience using the drug could be administered. The PMMP achieved a good level of response from patients in several studies but was unsustainable based on research grants because the data collection process was time consuming and required a significant number of competent staff. If sufficient funding for an extensive time period was available, the PMMP would provide a proactive surveillance method that could incorporate a conditional drug approval process leading to better safety and cost-effectiveness data on which to base final decisions about the listing of drugs.

As a longer-term strategy, continuing education about ADRs and the need to report them is key to improving under-reporting. This has been promoted by experts in pharmacovigilance[37] and randomized trials comparing physicians' and pharmacists' reporting rates before and after training on ADR reporting have demonstrated the benefit of education.[38,39] Health Canada makes efforts to educate healthcare providers and consumers about the SRS and to encourage them to use it. However, the agency's focus seems to be on increasing the number of ADR reports as though a greater number is the sole goal of the monitoring system. Less emphasis seems to be placed on encouraging high quality reports. More ADR reports of low quality or repetition of reports from different sources are unlikely to reduce drug safety risks.

ADR reporting is higher when the attitude of healthcare professionals towards it is more positive.[40-42] Therefore, education about appropriate prescribing, the recognition of ADRs and the duty to report them should be included at every opportunity in the training of healthcare professionals so that life-long habits are developed. However, relatively little time in the standard medical training curriculum is presently devoted to therapeutics, understanding drug safety and the responsibility of healthcare providers in reporting risks. Greater emphasis needs to be placed on training in these areas in the curricula of medical, pharmacy and nursing schools.

While training is crucial, the process for ADR reporting must also be improved. Many resources have been put into the development of electronic medical record systems to benefit patient care, but there appears to have been little attention devoted to integrating a simple and straightforward procedure to report an ADR within these systems. Intuitive, user-friendly, and easily accessible methods that are simple and quick to complete need to be incorporated within electronic medical record systems to place the process of reporting into day-to-day clinical practice.[30]

If the Canadian pharmacovigilance system remains one of merely collecting frequently-duplicated ADR reports of doubtful quality and reporting numbers of ADRs (rather than rates), healthcare professionals and decision makers will continue to find the system less effective than it needs to be. Without significant improvements in both healthcare provider education and the pharmacovigilance system in Canada, the ineffectiveness of the system will persist.

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