

# Drug safety: Side effects and mistakes *or* adverse reactions and deadly errors?

Trained surveillance personnel are needed to collect more comprehensive reports of adverse drug reactions across Canada.

**ABSTRACT: Adverse drug events are a leading cause of preventable patient harm. Patients can suffer from an adverse reaction to a drug, an improper dose, or a lack of drug treatment. Adverse drug reactions rank as one of the top causes of death and illness in the developed world and have huge socioeconomic significance. It is estimated that as few as 5% of all adverse drug reactions are reported to appropriate agencies. Underreporting is likely related to the time required to report and failure to recognize adverse drug reactions when they occur. Children are particularly vulnerable. Medication errors are estimated to account for more than 5% of hospital admissions, but can be reduced by using prevention strategies. Removing medications from the marketplace when they cause serious adverse drug reactions may not be the best therapeutic option. A better solution is to improve understanding of the mechanisms of adverse drug reactions and the characteristics of patients at risk. Active surveillance using trained clinicians will aid in determining causality and improving prevention.**

**A** striking feature of modern medicine is the debilitating and lethal consequences of adverse drug reactions (ADRs), which rank as one of the top 10 causes of death and illness in the developed world,<sup>1</sup> claiming 100 000 to 218 000 lives in the United States annually.<sup>2,3</sup> The direct medical costs of ADRs in the US are US\$30 to \$130 billion annually.<sup>1,2,4</sup> These estimates are even more meaningful when compared with other high-cost diseases such as diabetes (\$45 billion),<sup>5</sup> obesity (\$70 billion),<sup>6</sup> and cardiovascular diseases (\$199 billion).<sup>7</sup>

The safety of medication use is an international concern that has attracted the attention of policymakers and clinicians in the US, Europe, and Canada. However, despite awareness, it remains a problem of huge socioeconomic significance. Underreporting and failure to recognize ADRs when they occur seem to be key areas of deficiency.

Complicating the discussion of adverse events is the range of working definitions for drug errors and side effects (see **Table**). A medication-related error is a good example of an adverse drug event (ADE). In all cases ADRs are ADEs, but an ADE does not necessarily become an ADR. For ex-

ample, an ADE that results from a dosing error does not become an ADR if the patient does not suffer any ill effects.

## Patient safety reporting systems

The Federal Drug Administration (FDA) and Health Canada have established ADR reporting systems for health professionals. However, these are passive systems that rely on voluntary participation and are thus characterized by low levels of reporting and limited clinical utility. Most critically, these passive surveillance systems are focused on drug regulatory frameworks and are not designed to provide clinicians and patients with evidence that is necessary to support safer medication use. These shortcomings were illustrated in a 1999 review of the FDA's

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Dr Carleton is associate professor in the Faculty of Pharmaceutical Sciences at the University of British Columbia. He is also director of the Pharmaceutical Outcomes and Policy and Innovations Programme at Children's and Women's Health Centre of British Columbia, and senior clinician scientist at the Child and Family Research Institute in Vancouver. Ms Smith is manager of the Pharmaceutical Outcomes and Policy and Innovations Programme.

**Table. Concepts and definitions.**

Concept	Definition
Adverse drug reaction (ADR)	A noxious and unintended response to a drug which occurs at doses normally used or tested for the diagnosis, treatment, or prevention of a disease or the modification of an organic function. <sup>8</sup>
Adverse drug event (ADE)	An event leading to injury of a patient relating to the utilization of a drug. <sup>9</sup>
Injury	Any adverse effect caused by drug alone and any negative effects caused by the events or systems associated with the drug's use. <sup>9</sup>

handling of ADR reports by the Office of the Inspector General, which noted that “Even though it is the principal consumer protection agency in the federal government, the FDA does not have a comprehensive system in place to accurately identify the number of ADRs that are associated with the use of FDA-regulated products, nor to evaluate the cause of these incidents and the strategies to avoid similar future incidents from occurring.”<sup>10</sup> While the FDA’s MedWatch office was designed to facilitate voluntary reporting of ADRs, the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) found that as few as 5% of all ADRs each year are reported to appropriate authorities.

An equally serious challenge for clinicians who report ADRs involves separating the relative contributions of drugs and disease process to a patient’s chief complaint. Regulatory-based passive surveillance systems are not set up to provide practical assistance with interpretation of possible ADRs, and as a result many go unrecognized.<sup>11</sup> Similarly, systems that exist to record ADEs in institutions, such as incident reporting systems, are also passive in nature and require recognition and reporting of the event for pragmatic outcomes.

### Underreporting of ADRs

The extent of underreporting of serious ADRs was recently examined in Canada.<sup>12</sup> This study highlighted the failure to report toxic epidermal necrolysis, a well-established and life-threatening reaction primarily resulting from drug exposure. In order to derive an accurate estimate of the incidence of this reaction in Canada, the authors used data from two sources for the years 1995 to 2000: Canadian burn treatment centres and the Canadian Institute for Health Information (CIHI). They found that only 4% to 10% of cases identified were reported to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP).

In 2004, CADRMP received 10 238 reports of suspected adverse drug reactions for all ages. Of these reports, 7000 (68.4%) were classed as serious. The majority of reports (59.7%) originated from the manufacturers, 35.3% came from regional ADR centres, and the remaining 5% (507) came from the following groups: professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists, and patients.<sup>13</sup>

The well-documented lack of post-marketing ADR reporting by clinicians occurs despite claims by health

care organizations that drug safety is among their highest priorities. The National Survey on Child and Youth Healthcare Safety published this year by the Canadian Association of Paediatric Health Centres (CAPHC)<sup>14</sup> indicates that 82.1% of 28 participating institutions have mandatory reporting of all ADRs, and 70.4% have mandatory reporting of all serious and life-threatening adverse events, while 60.7% of institutions cited serious and life-threatening ADRs to be a safety issue of concern. The effect of this apparent concern has been minimal, however, as few reports of ADRs find their way to reporting agencies.

The reasons for ADR underreporting are complicated, but are likely related to the time requirements for reporting as well as the difficulty of recognizing ADRs when they occur. Clinicians may believe another member of the health care team will report the reaction; patients and clinicians may not know how or where to report; patients and clinicians may not recognize the ADR as such because direct causality of an ADR can be difficult to determine. Unfortunately, information provided in ADR reports is often insufficient to properly establish the relationship between drug and adverse outcome.

Health Canada recently commissioned Decima Research to conduct a public opinion survey on key issues pertaining to postmarket surveillance of health products in Canada.<sup>15</sup> This survey focused on views and opinions of the effectiveness of Health Canada’s methods to communicate health product safety information and the perceived utility of compulsory ADR reporting. Between March and August 2003, 1500 members of the public and 551 health professionals were surveyed. The responses to the survey revealed the following information:

- Consumers have a limited under-

standing of the drug safety system and rely on health professionals.

- Health professionals are not familiar with resources concerning drug safety information.
- Consumers are more concerned with treatment of ADRs than with reporting.
- Consumers support mandatory ADR reporting by clinicians.
- Few health professionals have reported an ADR.
- Many professionals recognize the seriousness of both the problem of ADRs and the lack of reporting.

Results of focus groups conducted with clinicians at the Children's and Women's Health Centre of British Columbia in January 2005 suggest that ADR reporting by clinicians would be best supported in clinical practice environments as part of an interactive dialogue between the identifying clinician and trained surveillance personnel. Clinicians who report ADRs and patients who experience them should receive direct benefits in terms of increased understanding of the problem as well as possible solutions that are directly relevant to an individual or institutional practice. In other words, there must be a positive clinical consequence for the collective effort of comprehensive surveillance.

### **ADRs in children: Therapeutic orphans**

Of particular concern is the alarming lack of understanding of ADRs in children, despite widespread use of drugs in this patient population. A recent examination of pediatric administrative data from Canadian private drug payment plans showed the extent of pediatric medication use—approximately 50% of about 2 million eligible children had been prescribed medications.<sup>16</sup> This estimate of medication use is corroborated by BC PharmaNet data (1998 to 2001), which indicate

that, on average, over 530 000 children (approximately 54% of BC children) were dispensed at least one prescription medication annually. (PharmaNet is British Columbia's fully comprehensive prescription data utilization database, which includes information about drugs purchased in the community, but not those used in hospitals.)

While children are known to be at greater risk than adults, there is a

reacted to medications as if they were "small adults." Clinical practice focused on adjusting dosage to account for smaller body mass, with the assumption that clinical effects would be equivalent to those observed in adults. It is now understood that a host of biological, developmental, and behavioral factors affect the safety and effectiveness of pharmaceuticals when used in pediatric patients. In addition,

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remarkable lack of understanding of causation, and therefore limited ability to avoid or prevent these occurrences. Alarming, between 13.7% and 16.6% of pediatric hospitalizations result in ADRs, and 27.9% of these reactions are severe.<sup>17,18</sup> Each year, approximately 26 500 American children (to age 18 years) die from ADRs.<sup>1</sup> Health Canada's records show health care providers and pharmaceutical manufacturers reported 1193 ADRs in children between 1998 and 2002. However, this voluntary reporting system unquestionably reflects only a small proportion of significant ADRs.

More than 75% of pharmaceuticals licensed in North America have never been tested in pediatric populations and are used without adequate guidelines for safety or efficacy.<sup>19</sup> Until recently, it was assumed that children

children often cannot verbalize their own drug therapy experiences.

An essential component of post-natal development is the acquisition of increasing drug biotransformation capacity, which manifests in distinct pathway and isoform-specific patterns.<sup>19</sup> Developmental changes in drug-metabolizing enzyme activities can be observed clinically as age-dependent differences in drug clearance or dosing requirements. For example, midazolam plasma clearance, which primarily reflects hepatic CYP3A4/5 activity after intravenous administration, increases approximately sevenfold (1.2 to 9.0 mL/min/kg) over the first 3 months of life. Carbamazepine plasma clearance, also largely dependent upon CYP3A4, is greater in children than in adults, thereby necessitating higher weight-adjust-

ed (mg/kg) doses of the drug to produce therapeutic plasma concentrations.

It is for these kinds of reasons that children worldwide are described as “therapeutic orphans.” Newborns, infants, and children who require medication for acute, chronic, and lifesav-

on systems. Four subcultures within an organization are necessary to support this: a reporting culture, a just culture, a flexible culture, and a learning culture.

High-reliability organization theory posits that accidents occur because individuals who operate and manage

to learn, to evaluate, and to change processes before the next error occurs. But of course, this can only be accomplished if these opportunities are recognized.

### Next steps

Removing medications that cause serious ADRs from the marketplace has been a common strategy to ensure patient safety. This is not always the best solution, as in many cases it may leave seriously ill patients without the benefits of therapy. A better solution lies in finding the mechanism for these ADRs and defining characteristics of patients who experience these ADRs, so that use can continue for patients who benefit from the medication and risk management strategies can be instituted.

Recent discussions in Canada have raised the prospect of federal legislation for mandatory reporting of ADRs. Our experience suggests that this might not generate accurate ADR incidence rates because mandatory reporting, like voluntary reporting, relies on clinicians’ ability to recognize ADRs and identify drug causality. We believe a more promising and practical approach to this problem is a large-scale epidemiological examination of ADRs through an active surveillance process whereby trained clinicians monitor and report ADRs. This strategy would be distinct from the current voluntary reporting approach and would rely on reporters whose principal and perhaps even sole responsibility is the identification and case ascertainment of ADRs. Dedicated, trained surveillance personnel with primary responsibility for ADR reporting at health care institutions across Canada are needed. These surveillance personnel would collect more comprehensive ADR reports, including detailed outcomes for each case, and would also aid in determina-

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ing treatment are at risk of a range of ADRs, from ineffective treatment and minor reactions to severe morbidity and death.<sup>19,20</sup>

### Drug errors

In the United States, it is estimated that medication errors are behind 5.6% of hospital admissions.<sup>21</sup> Medication error prevention strategies have shown that some reduction in errors can be achieved. Prevention strategies include mandating institutional standards to prevent errors in hospitals and pharmacies,<sup>22</sup> improving working conditions to prevent worker fatigue<sup>23,24</sup> and restricting medication-related practices to certain health care professionals.<sup>25</sup>

Two paradigms have been suggested to explain precursors to medication errors and develop interventions to prevent them: accident theory and high-reliability organizational theory.<sup>26</sup> Accident theory proposes that errors result from system failure and thus there is a need for a system that collects, analyzes, and disseminates information from incidents and near misses and makes regular proactive checks

complex systems are not themselves sufficiently complex to sense and anticipate the problems generated by the system. Safety cultures appear to be supported when there is:

- Recognition of conflicting incentives.
- Provision of sufficient resources for developing information systems and reporting requirements.
- Acknowledgment that errors will occur and their impact on patients, families, and health care providers will need to be dealt with.

Benjamin<sup>27</sup> supports the idea that minimizing errors also requires the health care team to be involved in early and continuous training to recognize and prevent errors and make use of advances in technology (e.g., bar coding, computerized health records), and that organizations be willing to commit health care resources to this endeavor. Acknowledging problems and overcoming the institutional culture of blame are of critical importance.

The good news is that drug errors do not always have an adverse clinical consequence, and that these near misses provide truly golden opportunities

tion of ADR causality and lead preventability assessments and other ADR-based initiatives. Currently, the causal link between the administration of a drug and the reaction is rarely known or estimated with precision. Understanding causality and preventability of ADRs will significantly aid in better therapeutic monitoring for patients receiving a drug therapy known to carry risks.

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#### Competing interests

None declared.

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