

ADVERSE DRUG EVENTS - WHY WE CARE

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ABSTRACT

Adverse drug reactions (ADRs) play an important role in the rational and safe use of medicines. ADRs occur in 10% of patients prescribed a medicine in the primary health care setting. Approximately five percent of all hospital admissions are due to an ADR and 10% of patients in hospital will develop an ADR. ADRs are a major burden on often stretched healthcare systems, with substantial economic impact. Many ADRs are preventable and an awareness of these risks are paramount in terms of the prevention of patient harm.

This article will provide a broad overview of the epidemiology of ADRs, their costs to the healthcare system, a simple classification for ease of recognition, causality assessment and the importance of pharmacovigilance as well as ADR reporting.

INTRODUCTION

According to the World Health Organization, an adverse drug reaction (ADR) is any noxious, unintended and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy.¹

EPIDEMIOLOGY OF ADRs

ADRs occur commonly. In the primary care setting approximately 10% of patients who are prescribed medicines will experience an ADR. ADRs are associated with an increase in morbidity, mortality as well as in hospitalisations.^{2,3,4} A landmark study in ambulatory patients in the USA found that for every \$1 spent on a drug, \$1.13 was also being spent due to an ADR.^{5,6} About 5% of medical admissions have been attributed to ADRs and about 10% of patients will develop an ADR in-hospital depending on the type of hospital, definition of an ADR, and the study methodology.^{2,3,4,7,8} The incidence of serious and fatal ADRs in hospitalised patients has been reported to be as high as 6.7% and 0.32%, respectively.^{8,9,10}

Although there is limited local ADR data, a recent hospital South African survey found that ADRs contributed to the death of 2.9% of hospitalised patients.¹¹ Studies emanating from high income countries indicate that ADRs are in the top 10 causes of death. Importantly, studies have shown that up to 50% of ADRs are potentially avoidable.^{4,10} Common errors resulting in ADRs include failure to illicit patients' allergies, errors in prescribing or dispensing, inadequate monitoring of patients and failing to recognise important drug-drug interactions.^{5,7,9,12}

The economic impact of ADEs is substantial and potentially avoidable.^{8,13,14} ADRs and their subsequent comorbidities

lead to increased hospital costs. Depending on facility size, hospital costs annually for all ADRs, are estimated to be as much as \$5.6 million per hospital.^{9,14} Patients who experience ADRs have longer, more expensive hospitalisations than patients who do not suffer ADRs. This leads to a large drain on resources, not only financial but human as well.^{13,14,15}

CLASSIFYING ADRs

Although most ADRs can be anticipated, others are unpredictable, especially rare idiosyncratic reactions.

ADRs are categorised into type A, B, C, D, E and F reactions.^{16,17} This paper will focus on the more common ADRs, i.e. A and B.

Type A reactions are expected amplifications of a drug's known pharmacologic effects. They usually are dose-dependent, predictable and in most cases, preventable. Type A reactions are responsible for the majority of ADRs encountered. Examples include hypotension with antihypertensive agents and anticholinergic effects with tricyclic antidepressants.^{16,17,18} Type A reactions tend to occur in patients who have one of three characteristics. Firstly, the patients usually have received a higher than normal dose. Secondly, they may have received the normal dose of the drug, but they may metabolise or excrete the drug more slowly, leading to drug plasma levels that are too high, possibly due to concomitant disease or drug-drug interactions.^{16,17} A good example would be the administration of simvastatin with the anti-retroviral protease inhibitor, ritonavir. This interaction, leads to a 25-fold increase in the simvastatin plasma level with the resultant increased risk of rhabdomyolysis.¹⁹

Thirdly, they may have normal drug plasma levels but are sensitive to their pharmacological effects, e.g. the elderly are more sensitive to the pharmacological actions of the neuroleptics. Most type A reactions are usually identified prior to drug marketing and may be listed in the package insert of the medicine.^{16,17}

Type B reactions are idiosyncratic and tend to be unrelated to the known pharmacologic action of the drug. They are usually not related to dose, unpredictable, uncommon and potentially clinically more serious than type A reactions.^{16,17,18} Type B reactions may be due to a hypersensitivity or immunologic reaction. These are characterised by immune-mediated organ disease. Haptenisation of the organ cells by the parent drug or metabolite occurs. Presentation via major histocompatibility complex class II leads to immune activation and cellular toxicity, by T/B-lymphocytes and Natural Killer cells.²⁰

The *non-allergic* ADRs may involve the covalent binding of a reactive drug metabolite to cells causing cell death.²¹

These reactions often concentrate in certain body systems, including the liver, blood, skin, kidney and nervous system. A typical example of a type B ADR is anaphylaxis due to the administration of penicillin.

Because type B reactions are uncommon or rare, they are often only detected after marketing of a drug. Type B reactions represent a major focus of pharmaco-epidemiologic studies of ADRs.^{16,17,18}

PHARMACOVIGILANCE

Because ADRs represent an important public health concern as well as cost, the science of pharmacovigilance has been developed.¹⁸ Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines. It is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare workers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to:^{18,22}

- Identifying new information about hazards associated with medicines;
- Preventing harm to patients.

There are important limitations of the safety data of newly marketed drugs. Pre-marketing randomised controlled trials are mainly performed for regulatory purposes. They lack sufficient power to detect uncommon or rare ADRs, and have strict inclusion criteria. These criteria exclude patients who will commonly be given the drug (e.g. elderly, those with kidney and liver impairment), and are unable to detect long term cumulative toxicity (e.g. the long term increased risk of cardio-vascular disease from non-steroidal anti-inflammatory drugs was only recognised after more than 50 years of use).^{18,22}

Spontaneous reports of drug-related morbidity or mortality by healthcare workers are often the first signal of a new ADR. In some countries there is a strong culture of spontaneous reporting among healthcare workers, often with particular drugs selected by national regulatory bodies. Spontaneous reports of potential new ADRs are captured by an international centre to ensure maximum chances of detection.^{6,18} Signals from spontaneous reports are usually studied with observational case-control or cohort studies. However, observational studies are limited by confounding, which is the possibility that the apparent effect of a drug exposure is due to other factors.¹⁸ Only randomisation can control for confounding, but it is seldom possible to conduct a randomised controlled trial to confirm whether there is cause-effect relationship between exposure to the drug and an event.¹⁸

Current methods of pharmacovigilance responsible for ADR recognition and prevention, have failed to detect some serious adverse effects.^{7,18,22} Strategies to prevent ADRs requires identification of the significant risk factors, while signal detection requires ongoing review of ADR reports and early causality assessments.¹⁸

Criteria have, therefore, been developed to help determine the strength of association between drug exposure and an adverse event. Several systems have been developed for causality assessment. A commonly used system is provided in Table I which may be helpful in clinical decision making.²²

ADRs should also be classified by severity, which may help predict clinical and/or drug regulatory action.^{18,22}

- *Minor*: No antidote, therapy or prolongation of hospitalisation is required;
- *Moderate*: Requires a change in drug therapy, specific treatment, or an increase in hospitalisations by at least 1 day;
- *Severe*: Potentially life-threatening, causing permanent damage, or requiring intensive medical care;
- *Lethal*: Directly or indirectly contributes to the death of the patient.

Regulatory actions include the addition of a new contra-indication and updated warnings or special precautions in order to allow for the safer prescription and administration of the drug. A further, but more difficult regulatory action would be the removal of a labelled indication when the risk-benefit profile is deemed to be unfavourable.

CONCLUSION

ADRs are an important cause of morbidity and mortality. They have major clinical, public health and economic implications. The majority of ADRs are related to the pharmacological action of the drug (type A) and are often preventable. This highlights the importance of rational drug selection, always weighing up the risks against the benefits.

TABLE I: ADR CAUSALITY ASSESSMENT SCALE

QUESTIONS	RESPONSE SCORE #	
	YES	NO
Are there previous conclusive reports on this reaction?	+1	0
Did the adverse event appear after the suspected drug was given?	+2	-1
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0
Did the adverse reaction appear when the drug was re-administered?*	+2	-1
Are there alternative causes that could have caused the reaction?	-1	+2
Did the reaction reappear when a placebo was given?	-1	+1
Was the drug detected in any body fluid in toxic concentrations?	+1	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0
Score interpretation	>9 = definite ADR 5-8 = probable ADR 1-4 = possible ADR 0 = doubtful ADR	

Score 0 if unknown or not done.

* Note that rechallenge is seldom justified

(adapted from Naranjo CA et al. A method of estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45)

Increased awareness of ADRs and the requirement to report will undoubtedly decrease the burden of ADRs and improve patient outcomes.

DECLARATION OF CONFLICT OF INTEREST

The author has no conflict of interest to declare.

REFERENCES

- Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. *BMJ* 1998;316:1295-1298.
- Lagnaoui R, Moore N, Fach J, Mongy-Boursier M, et al. Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *Eur J Clin Pharmacol* 2000;55:181-6.
- Bond CA, Raehl CL. Adverse drug reactions in United States Hospitals. *Pharmacotherapy* 2006;26(5):601-8.
- Runciman WB, Roughhead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. *International Journal for Quality in Health Care* 2003;15(1):i149-i159.
- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279(15):1200-5.
- Psaty BM, Burke SP. Protecting the health of the public - Institute of Medicine recommendations on drug safety. *N Engl J Med* 2006;355:1753-1755.
- Mehta U, Durrheim DN, Blockman M, Kredt T, et al. Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. *Br J Clin Pharmacol* 2008;65(3):396-406.
- Classen DC, Pestotnik SL, Evans RS, Lloyd JF, et al. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1997;277:301-6.
- Moore N, Lecoitre D, Noblet C, Mabilie M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol* 1998;45:301-308.
- Pirmohamed M, James S, Meakin S, Green C, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. *BMJ* 2004;329:15-19.
- Mouton JP, Mehta U, Parrish AG, et al. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. *Br J Clin Pharmacol*, doi: 10.1111/bcp.12567
- Phillips DP, Christenfeld N, Glynn LM. Increase in US medication-error deaths between 1983 and 1993. *Lancet* 1998;351:643-4.
- Lopez AD, Mathers CD, Ezzati M, Jamison DT, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;367:1747-1757.
- Bates DW, Spell N, Cullen DJ, Burdick E, et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. *JAMA* 1997;277(4):307-11.
- White T, Arakelian A, Rho JP. Counting the cost of drug-related adverse events. *Pharmacoeconomics* 1999;15:445-458.
- Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ* 2003;327:1222-1225.
- Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. *Lancet* 2000;356:1255-1265.
- Pillans PI. Clinical perspectives in drug safety and adverse drug reactions. *Expert Rev Clin Pharmacol* 2008;1(5):695-705.
- Fichtenbaum C, Gerber J, Rosenkranz S et al. Pharmacokinetic interactions between protease inhibitors and selected HMGCoA reductase inhibitors. Paper presented at Seventh Conference on Retroviruses and Opportunistic Infections. San Francisco, CA; 2000 Jan 30-Feb 2
- Larson AM. Drugs and the liver: Metabolism and mechanisms of injury. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Last Accessed on September 4th, 2015.)
- Kaplowitz N. Idiosyncratic drug hepatotoxicity. *Nat Rev Drug Discov* 2005;4(6):489-99.
- Naranjo CA et al. A method of estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45.