Assessing, managing and reporting adverse drug reactions may better equip us to minimise medicines-related harm

All health professionals should be alert to the possibility that medicated patients in their care may experience an adverse drug reaction. In this article Anthony Cox describes how to fully characterise an adverse drug reaction, highlighting that this will reveal the most appropriate management strategy. By reporting adverse events to the regulatory authorities prescribers will be better equipped with the information needed to minimise future incidents of medicines-related harm.

Introduction

Because all medicines have the potential to cause adverse effects, the safety of prescribed medicines is a central concern for health professionals. The initial decision to resort to pharmacological treatment, the choice of drug, and the management and monitoring of the patient require knowledge of drug-induced disease. Additionally, a wider public health duty exists for the prompt detection of new adverse drug reactions (ADRs).

The first attempt to fully describe the adverse effects of a drug was undertaken by William Withering in his 1785 treatise on digitalis.[1] However, drug withdrawals and safety concerns have continued to occur, illustrated by recent concerns about cardiac events associated rosiglitazone,[2] the possibility of psychiatric illness associated with varenicline[3] and the withdrawal of lumiracoxib due to cases of unpredictable liver failure.[4]

Definition of an adverse drug reaction

Clear definitions are important.[5] The terms adverse effect (of the *drug*) or adverse reaction (of the *patient*) can be used interchangeably. The World Health Organisation defined an adverse drug reaction (ADR) as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological functions'.[6]

© *Jeffrey Smith/ istockphoto*

This definition excludes the toxic effects of drugs caused by poisoning.

Importantly, it also does not imply any knowledge of a clear pharmacological link between the drug and the event.

A revised definition of an ADR was provided by Edwards and Aronson[7] to address deficiencies of the WHO definition, such as its failure to consider reactions caused by herbal substances, excipients and contamination, and the potential for medical error to induce an ADR. Their definition is: 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regime, or withdrawal of the product'.[7]

The term side-effect has been used to denote unintended effects, either beneficial or adverse, which are related to the pharmacological properties of a drug. Although this term continues to be used in the *British National Formulary*, its use should be discouraged to avoid confusion in terminology.[8]

Central to the definition of an ADR is the suspicion of a causal relationship

Basic pharmacy skills

between the drug and the adverse event. Events that occur after the administration of a drug, with or without such a relationship, are termed adverse drug events (ADEs). It therefore follows that all ADRs are ADEs, but not all ADEs are ADRs. This distinction is of particular importance when assessing drug safety literature.

The burden of iatrogenic disease
Although media attention often focuses on the safety of new drugs, the major causes of admissions to hospital are older-established drugs with relatively well-described safety profiles. The most reliable UK study investigating this showed that 6.5% of hospital admissions involved an ADR, the most common being caused by NSAIDs, aspirin, warfarin or diuretics.[9] The projected economic costs of ADR-related admissions to hospitals was estimated to be £466 million. More than 6% of inpatients may also experience an adverse drug event.[10] Consultations involving ADRs for general practitioners are estimated to be 1.7%.[11]

Identification of ADRs
ADRs can be detected by several methods. In primary care, patients may suspect ADRs and raise their concerns with their general practitioner or community pharmacist, but less obvious effects can easily be misinterpreted. Reliable drug history-taking is essential to detect potential ADRs — with temporal associations being a strong indicator for a potential ADR. Specific
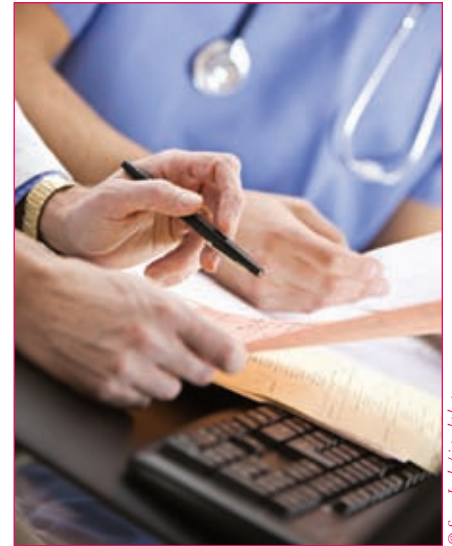
© Sean Lockel / istockphoto

questions may be required to obtain information about over-the-counter drug use, skin and ocular preparations and about herbal products.

Pharmacists should also be vigilant for drugs that may have been prescribed to treat potentially drug-induced symptoms. Patient observation and communication are also important, and can lead to the detection of potentially drug-induced effects, such as jaundice or tremor.

Formal causality assessments are not commonly carried out in clinical practice, and re-challenge with a drug that may be suspected to have caused harm has ethical problems.[12] However, de-challenge by withdrawal of a drug and subsequent relief of symptoms may indicate the presence of an ADR. In addition, screening for ADRs using biochemical results can identify significant ADRs. An example being drug-induced hyperkalaemia, caused by drugs such as spironolactone, ACE inhibitors or nebulised beta-agonists.

Assessment and classification of ADRs
The classification of ADRs has most commonly been undertaken using the Rawlins and Thompson system,[13] which separates ADRs into one of two types of reaction. Type A reactions are dose-dependent pharmacologically predictable reactions and Type B reactions are non-dose

---

Table 1. DoTS system of ADR classification*

Dose-relatedness	Time relatedness	Susceptibility
Toxic effects: ADRs that occur at doses higher than the usual therapeutic dose. **Collateral effects:** ADRs that occur at standard therapeutic doses. **Hypersusceptibility reactions:** ADRs that occur at subtherapeutic doses in susceptible patients.	**Time independent reactions:** ADRs that occur at any time during treatment. **Time dependent reactions:** *Rapid reactions* occur when a drug is administered too rapidly. *Early reactions* occur early in treatment then abate with continuing treatment (tolerance). *Intermediate reactions* occur after some delay, but if reaction does not occur after a certain time little or no risk exists. *Late reactions* — risk of ADR increases with continued-to-repeated exposure, including withdrawal reactions. *Delayed reactions* occur some time after exposure, even if the drug is withdrawn before the ADR occurs.	Raised susceptibility may be present in some individuals, but not others. Alternatively, susceptibility may follow a continuous distribution — increasing susceptibility with impaired renal function. Factors include: genetic variation, age, sex, altered physiology, exogenous factors (interactions) and disease.

*DoTS= Dose-relatedness, timing and patient susceptibility; ADR= Adverse drug reaction

Table 2. Examples of the application DoTS to specific ADRs

ADR	Dose	Time	Susceptibility	Management implications
Penicillin anaphylaxis	Hyper-susceptibility	First dose	Not, understood, but requires sensitisation	Avoid penicillins in susceptible individuals
Adrenal crisis following withdrawal of oral corticosteroids	Collateral effect	Late reaction	All are susceptible	Withdraw long-term oral corticosteroids slowly
Nitrate headache	Collateral effect	Early reaction	No predictable susceptibilities	Counsel patient about the risks of headaches on starting treatment
Digoxin toxicity	Toxic effect/collateral effect (in presence of hypokalaemia)	Time independent	Renal impairment, hypokalaemia	Monitor digoxin levels, potassium levels and serum creatinine
Lumiracoxib	Collateral/toxic effect (more common at high doses)	Time independent	No predictable susceptibilities	Withdrawal of drug from market

dependent and unpredictable in nature. Although the simplicity of this classification is helpful, this system hides, rather than reveals, details of a reaction. Properties of the affected individual (genetic, pathological, and susceptibility), and the time-course and severity of the reaction are not taken into account.

To address this deficiency, Aronson and Ferner have proposed a three-dimensional classification system based on dose-relatedness, timing and patient susceptibility (DoTS).[14] The dose-relatedness, timing and patient susceptibility of an adverse reaction are classified by application of the criteria shown in Table 1.

Using this system an ADR can be profiled in such a way that implications for management of the ADR may be more obvious. For example, red man syndrome caused by the rapid injection of vancomycin,[15] can be characterised as a collateral time-dependent rapid reaction, with no specific susceptibilities. Future management would therefore focus on following the correct advice on administration at a rate not greater than 10mg per minute. The dystonic reactions to metoclopramide can be characterised as a collateral time-dependent reaction, with both sex and age acting as susceptibilities. Future management would therefore focus

on avoiding the use of the drug in susceptible groups such as children and young women. Other examples of the application of this classification system are set out in Table 2.
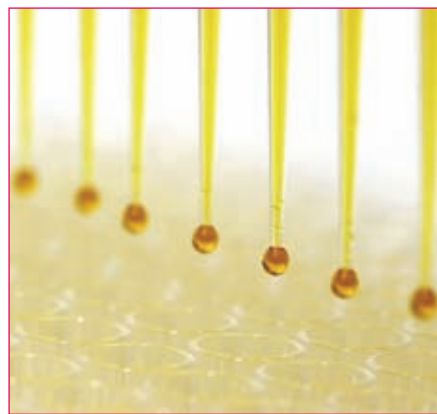
Avoiding ADRs
Established drugs are responsible for the greatest burden of drug-induced morbidity and mortality. Therefore rational and appropriate prescribing is of key import-

© Dra Schwartz / istockphoto

ance. The risk of some ADRs can be mitigated or eliminated by avoiding use of the drug or by taking suitable precautions in those patients with contra-indications or cautions for drug use. For example, the MHRA stated that more than 50% of reports they received of patients who had seizures associated with bupropion had

predisposing factors for seizures, such as a past history of seizures or other drugs known to reduce the seizure threshold.[16]

In those in whom drug use is necessary the appropriate use of concomitant treatments to protect against ADRs may be needed, such as proton pump inhibitors with NSAIDs. However, despite precautions being taken to avoid ADRs not all cases are preventable. The use of a prescribed drug is an acceptance that harm may be caused to an individual patient even if the desired effect is more likely.

Monitoring of therapy through drug or biochemical testing provides an opportunity to prevent ADRs. However, published trials and manufacturers' information frequently do not provide sufficiently robust evidence for logical monitoring schemes.[17] Therefore, such schemes may be unable to detect an adverse drug reaction before harm is done. For example, in the case of hyperkalaemia associated with the use of spironolactone in heart failure practitioners may feel that initial frequent monitoring of potassium levels will detect those patients who are likely to develop hyperkalaemia. However, a significant proportion of cases occur more than three months after treatment has started.[18] The optimal monitoring frequency may, therefore, be difficult to elucidate.

Basic pharmacy skills

> Impaired renal or hepatic function — either because of declining physiological function or natural individual variation in response — can increase the risk of ADRs. Due regard should be taken of the individual characteristics of drug responses to these disease states in order to chose the most appropriate drug and dose.

Impaired renal or hepatic function — either because of declining physiological function or natural individual variation in response — can increase the risk of ADRs. Due regard should be taken of the individual characteristics of drug responses to these disease states in order to chose the most appropriate drug and dose.

The elderly are more prone to having adverse reactions,[19] but this can be related to their generally higher levels of co-morbidities, polypharmacy, and to declines in physiological function, rather than to chronological age *per se*. The young may be at higher risk of ADRs because of differences in drug metabolism and elimination, and end-organ response. Chloramphenicol, digoxin and ototoxic antibiotics such as streptomycin are examples of drugs that have a higher risk of toxicity in the first weeks of life. Older children and young adults may also be more susceptible to ADRs; a classic example of this in young people is the heightened risk of metoclopramide producing extrapyramidal effects.[20] Children may have an increased risk of ADRs linked to the heightened possibility of dosing errors combined with a relative lack of evidence for safety and efficacy.

Women may be more susceptible to several ADRs.[21] Ethnicity has also been linked to susceptibility to ADRs.[22] Examples include the increased risk of angioedema with the use of ACE inhibitors in black patients, and the increased propensity of white and black patients to experience central nervous system ADRs

associated with mefloquine in comparison with patients of Chinese or Japanese origin. However, race or ethnicity can be argued to be a poor marker for the biochemical genotype of a patient.[23]

Pharmacogenomics, the study of genes that influence individuals' responses to drugs, has yet to deliver on an appreciable scale the reduction in ADRs that many predicted. However, examples of severe ADRs exist that can be avoided with knowledge of a patient's genetic susceptibility. Recently, the Food and Drug Administration (FDA) advised of an increased risk of severe skin reactions (such as toxic epidermal necrolysis and Stevens–Johnson syndrome) associated with carbamazepine

© Lise Gagné/ istockphoto

in South East Asian populations (including those from China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan, and to a lesser extent Indians and the Japanese).[24] The presence of leukocyte antigen (HLA) allele, HLA-B*1502, for which genetic testing is already available, indicates an increased risk of skin reactions. Carbamazepine is best avoided in this group of patients.

Advice to patients on the correct use of their medication, and early warning signs of severe reactions can help mitigate the worst outcomes of drug therapy. Examples include warnings of mouth swelling with ACE inhibitors (angioedema), unusual

bruising or bleeding with sulfasalazine (blood disorders), or signs and symptoms of liver failure with anti-tuberculosis treatment. However, many ADRs are not preventable because of the intrinsic nature of the drugs concerned or the continued difficulties in assessing the risk/balance in the use of medicines.

Management of ADRs

Treatment of ADRs is dependent on the type of reaction, the severity of the reaction, and the risk–benefit of continuation of therapy. Some drugs may need to be continued despite the presence of an adverse reaction; for example, anti-epileptics despite some symptoms of drowsiness. Other reactions may respond to a dose reduction, such as digoxin toxicity. Others will require the withdrawal of drug therapy.

Some mild ADRs may be indicative of a more severe reaction to come. A mild rash in a woman taking strontium ranelate may later progress to a drug rash with eosinophilia and systemic symptoms (DRESS), which has proved fatal in some cases.[25] Immediate drug withdrawal in such cases is warranted and treatment should not be re-started. In other cases staged withdrawals may be required because of the risk of withdrawal reactions.

Reporting adverse drug reactions

The Yellow Card scheme was started in 1964 in the wake of the thalidomide disaster. The scheme is a spontaneous reporting scheme — incidents are detected and reported by the health care professionals. There is no fee for reporting adverse reactions. For new drugs and vaccines under intensive surveillance — identified by the black triangle symbol — all suspected ADRs should be reported regardless of how trivial they may appear. For established drugs and vaccines, only serious suspected reactions should be reported. Serious reports include disability, life-threatening or deadly reactions, medically significantly reactions, such as bleeding or congenital birth defects. Further guidance on ADR reporting is given in the *British National Formulary* and at the MHRA Yellow Card reporting site http://www.yellowcard.gov.uk.

© Jeffrey Smith/istockphoto

Although under-reporting of ADRs to these spontaneous reporting systems is widespread,[26] spontaneous reporting continues to be of great importance in the detection of new ADRs.[27,28]

In the past 10 years there has been a large change in the reporting culture of the Yellow Card scheme, with the extension of the scheme to all health care professionals. More recently, patient reporting of ADRs has received increased attention. Although evidence is currently limited about the role of patient reporting of ADRs, declining health care professional reporting will make patient reports increasingly important in maintaining adequate levels of reports.[29] Pharmacists could also play an important role in facilitating the reporting of patient concerns to the Yellow Card scheme.

Conclusion

ADRs continue to place a considerable burden on the health of the nation. Knowledge and use of ADR classification systems can give the health professional greater clarity about an ADR and suggest ways of managing or avoiding a future event. Future drug safety depends on the vigilance of health care professionals in reporting suspected ADRs to regulatory authorities, and on facilitating patient reporting of ADRs. ✤

> Pharmacogenomics, the study of genes that influence individuals' responses to drugs, has yet to deliver on an appreciable scale the reduction in ADRs that many predicted. However, examples of severe ADRs exist that can be avoided with knowledge of a patient's genetic susceptibility.

Declaration of competing interests
The author declares that he has no competing interests.

Anthony R Cox, pharmacovigilance pharmacist, West Midlands Centre for Adverse Drug Reactions, City Hospital, Dudley Road, Birmingham, and Tutor, Department of Health and Life Sciences, Aston University, Birmingham.
Email: anthony.cox@swbh.nhs.uk

References

1. Aronson JK. *An cccount of the foxglove and its medical uses 1785–1985*. 1st ed. London: Oxford Medical Publications, 1985.
2. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine* 2007; **356:** 2457–71.
3. Medicines and Healthcare Products Regulatory Agency. Varenicline: possible effects on driving; psychiatric illness. *Drug Safety Update* 2007; **1(5):** 12.
4. Medicines and Healthcare Products Regulatory Agency. Lumiracoxib: suspension of market authorisations. *Drug Safety Update* 2007; **1(5):** 15.
5. Ferner RE, Aronson JK. Clarification of terminology in drug safety. *Drug Safety* 2005; **28(10):** 851–70.
6. World Health Organization. *International drug monitoring: the role of national centres*. Tech Rep Ser 1972; No 498.
7. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *The Lancet* 2000; **356:** 1255–9.
8. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Annals of Internal Medicine* 2004; **140(10):** 795–801.
9. Pirmohamed M, James S, Meakin S *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *British Medical Journal* 2004; **329:** 15–9.
10. Krähenbühl-Melcher A, Schlienger R, Lampert M *et al.* Drug-related problems in hospitals: a review of the recent literature. *Drug Safety* 2007; **30(5):** 379–407.
11. Millar JS. Consultations owing to adverse drug reactions in a single practice. *British Journal of General Practice* 2001; **51:** 130–1.
12. Li Wan Po A, Kendall M. Causality assessment of adverse effects: When is re-challenge ethically acceptable? *Drug Safety* 2001; **24(11):** 793–9.
13. Rawlins MD. Clinical pharmacology: Adverse reactions to drugs. *British Medical Journal* 1981; **282:** 974–6.
14. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. *British Medical Journal* 2003; **327:** 1222–5.
15. Sivagnanam S, Deleu D. Red man syndrome. *Critical Care* 2003; **7(2):** 119–20.
16. Cox A, Anton C, Ferner R. Take care with Zyban. *The Pharmaceutical Journal* 2001; **266:** 718–22.
17. Coleman JJ, Ferner RE, Evans SJW. Monitoring for adverse drug reactions. *British Journal of Clinical Pharmacology* 2006; **61(4):** 371–8.
18. Anton C, Cox AR, Watson RD, Ferner RE. The safety of spironolactone treatment in patients with heart failure. *Journal of Clinical Pharmacology and Therapeutics* 2003; **28:** 285–7.
19. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. *British Journal of Clinical Pharmacology* 2004; **57(2):** 121–6.
20. Bateman DN, Rawlins MD, Simpson JM. Extrapyramidal reactions with metoclopramide. *British Medical Journal* 1985; **291:** 930–2.
21. Tran C, Knowles SR, Liu BA, Shear NH. Gender differences in adverse drug reactions. *Journal of Clinical Pharmacology* 1998; **38(11):** 1003–9.
22. Coleman JJ, McDowell SE. Ethnicity and adverse drug reactions. *Adverse Drug Reaction Bulletin* 2005; **234:** 899–902.
23. Cooper RS, Kaufman JS, Ward, R. Race and genomics. *The New England Journal of Medicine* 2003; **348(12):** 1166.
24. Food and Drug Administration. Information for Healthcare Professionals: *Carbamazepine (marketed as Carbatrol, Equetro, Tegretol and generics),* 2007. url: http://www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm [Accessed on the 17 January 2008].
25. Medicines and Healthcare Products Regulatory Agency. Strontium ranelate (Protelos): risk of severe allergic reactions. *Drug Safety Update* 2007; **1(5):** 15.
26. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: A systematic review. *Drug Safety* 2006; **29(5):** 385–96.
27. Olivier P, Montastruc JL. The nature of the scientific evidence leading to drug withdrawals for pharmacovigilance reasons in France. *Pharmacoepidemiology Drug Safety* 2006; **15(11):** 808–12.
28. Clarke A, Deeks J, Shakir SAW. An assessment of the publicly disseminated evidence of safety used in decisions to withdraw medicinal products from the UK and US markets. *Drug Safety* 2006; **29(2):** 175–81.
29. Blenkinsopp A, Wilkie P, Wang M, Routledge PA. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *British Journal of Clinical Pharmacology* 2006; **63(2):** 148–56.