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Competing financial interests
The author declares competing financial interests: see web version for details.

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A GUIDE TO DRUG DISCOVERY — OPINION

New approaches to drug safety: a pharmacovigilance tool kit

Lesley Wise, John Parkinson, June Raine and Alasdair Breckenridge

Abstract | The importance of pharmacovigilance — the ongoing assessment of the safety of a marketed medicine — has been increasingly appreciated in recent years, owing in part to high-profile safety issues with widely used drugs. In response, strategies to improve the collection, integration and analysis of data related to post-marketing drug safety are being initiated or enhanced. In this article, we summarize the key tools that are available for pharmacovigilance, discuss which might be the most appropriate to use in different situations and consider the future directions of the field.

When a new medicine is granted a marketing authorization, its clinical safety profile has been assessed on the basis of results from clinical trials. The number of patients recruited for these pre-marketing trials is usually calculated to ensure that differences in the efficacy of the new treatment compared with the control can be reliably detected. However, because any safety issues are likely to occur in a smaller proportion of patients than the positive effects of the treatment, the ability of these trials to detect harm is only reliable for the most common adverse reactions. This problem is exacerbated by the exclusion criteria for clinical trials, their short duration and the need to control other medications, which all make the clinical trial population unrepresentative of patients in routine clinical care. Only after a medicine has been used in less selected populations, and over longer periods, can its safety in routine care be comprehensively evaluated. This process of ongoing assessment of the safety of a marketed medicine throughout its life cycle is known as pharmacovigilance.

The aim of this article is to give a brief overview of some of the main data sources and methods in pharmacovigilance, considering both spontaneous adverse-reaction reporting systems and active surveillance. We then discuss how these might be used as a tool kit from which to select the most appropriate strategies for studying the safety profile of a given medicine in clinical use, taking into account the differences in the way such information is obtained and the circumstances under which patients studied are prescribed the medicine. Finally, we consider directions in which the field is moving.

Spontaneous reporting systems

Reports of adverse events that occur when a medicine is used in clinical practice form the basis of most pharmacovigilance systems, and most regulatory authorities operate a database for storing and analysing adverse-event reports. For example, the Medicines and Healthcare products Regulatory Agency (MHRA) operates the Yellow Card Scheme for health-care professionals, patients and carers to report suspected adverse drug reactions, and these reports are stored in the MHRA Sentinel database. The US Food and Drug Administration (FDA) operates a similar scheme, in which reports are stored in either the Adverse Event Reporting System (AERS) database or the Vaccine Adverse Events Reporting System (VAERS) database. In these systems, health-care professionals and patients are asked to report adverse drug reactions to regulatory authorities, and the pharmaceutical industry is obliged to submit reports of clinically serious reactions. These are essentially passive systems — that is, the patients are not selected to take part in a specific study and the reports are not actively solicited. The advantages and disadvantages of such systems are summarized in BOX 1.

In the past decade, several new statistical approaches have been used to improve the analysis of large databases of adverse-event reports, thereby permitting more rapid, robust and comprehensive detection of signals that indicate the possibility of safety issues[1]. Although the sophistication of such systems is an important advance, the inherent problems of spontaneous reports (BOX 1) remain, and automated systems can form only part of the analysis of reports. Following the identification of a safety signal, the reports leading to that signal need to be reviewed to evaluate the safety issue, including the frequency, causality mechanisms and preventability of the harm. If a potential safety signal is detected, further studies may be needed to allow interpretation of the data, and possibly to identify risk or protective factors to better inform prescribers and patients. These pharmacoepidemiological studies either follow a cohort of patients receiving a drug and a matched cohort not receiving the drug, looking for the relative rate of the potential adverse event, or follow those who have the event of interest and a matched group, and retrospectively assess whether they took the particular drug. For example, there were a number of reports of psychiatric symptoms in patients taking the smoking-cessation therapy varenicline (Chantix/Champix; Pfizer). The reports were reviewed and work was undertaken

to identify specific risk groups and update the product information for prescribers and patients. The matter was also highlighted to health-care professionals in various Drug Safety Update bulletins published by the MHRA (for example, see REF. 2).

Active surveillance

Active surveillance involves the identification of potential safety problems by the regular and systematic collection of clinical information on a specified population of patients that have been prescribed marketed medicines. There is no interference in the way that the drug is prescribed, and the study is carried out under normal clinical conditions of use of the drug. There are several ways in which this clinical information can be collected: patient registers, studies using databases of medical records, and clinical trials.

Patient registers (registries). These registers comprise a defined patient population on whom data is systematically collected for a defined period of time. The population may be defined either by specific drug exposure characteristics (drug registers) or by a specific condition (condition-specific registers). The aim of such registers is to increase the safety knowledge of the product, particularly in long-term use.

Drug registers may be based on a specific drug or a class of products. A recent example of a drug-specific register involves natalizumab (Tysabri; Biogen–Idec/Elan), a monoclonal antibody specific for integrin α4 that is used for the treatment of severe relapsing–remitting multiple sclerosis. Clinical trials and post-marketing data indicated that natalizumab was associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a potentially fatal disease of the central nervous system[3]. Natalizumab was voluntarily withdrawn from the market by the manufacturer in 2005 when the initial cases of PML associated with its use were identified. Following regulatory review of safety information and data on the benefits of the drug, natalizumab was reintroduced into the market in 2006 under a risk minimization programme in which patients receiving the drug are registered and monitored. The TYGRIS (Tysabri Global Observation Program in Safety) registry aims to recruit 6,000 patients worldwide, which will substantially increase the safety knowledge of the product.

An example of a drug class registry involves biologics that inhibit the inflammatory cytokine tumour necrosis factor (TNF) — etanercept (Enbrel; Amgen/Wyeth), infliximab (Remicade; Centocor/Schering–Plough) and adalimumab (Humira; Abbott) — which are widely used in the treatment of rheumatoid arthritis and psoriatic arthritis. Their use is also associated with an increased risk of severe infections and cancer, and the British Society of Rheumatology has established a register of patients who are being treated with these drugs, which is used to investigate possible adverse effects[4]. All patients in England who are prescribed one of these agents for rheumatoid arthritis must be included in the register, which now comprises ~25,000 patients. Similar biologics registries exist in other disease areas, such as the Biologics Registry of the British Association of Dermatologists.

The UK Epilepsy and Pregnancy Register provides a long-established example of a condition-specific register. Since 1966, this register has collected data on pregnant women with epilepsy, whether taking anticonvulsants or not, and who are referred before the outcome of the pregnancy is known, thereby avoiding selective reporting of pregnancies with adverse effects, which would constitute a form of bias[5]. This register provides important information on the risk of major congenital malformations that are associated with anticonvulsant drugs, and is invaluable in the development of national guidelines.

Other condition-specific registers include those set up to monitor treatment in rare conditions. The purpose of such registers is to be able to identify the impact of different treatments in the long term. As clinical trials of drugs for such diseases typically involve few patients, safety information can be limited. For example, idursulphase (Elaprase; Shire) is a treatment for Hunter's syndrome, a rare genetic disorder that occurs in approximately two people per million of the population in the European Union. Following marketing authorization of the product, Shire set up a registry known as The Hunter Outcomes Survey[6]. Every patient with Hunter's syndrome is encouraged to participate in the survey, regardless of whether they are being treated with idursulphase or not, as this will help provide information about the progression of Hunter's syndrome, disease management and medical outcomes.

Databases of medical records. Databases of records from medical practices or from community pharmacies can provide the basis for conducting epidemiological studies of drug safety, provided these databases contain details of drug exposure and records of outcomes in individual cases. The necessary information for such studies may be contained in a single database, in separate databases that are 'record-linked' or may be obtained directly from health-care professionals on the basis of the prescriptions they have issued.

Single databases include databases of primary-care records, such as the General Practice Research Database (GPRD) and the Health Improvement Network in the UK, and US health insurance databases from sources such as Group Health Cooperative of Puget Sound, Kaiser Permanente Medical Care Program and United Health Group. The databases generally contain details of diagnoses, treatments and their outcomes, hospital referral data and, in some cases, hospital data.

The FDA has recently announced the creation of a new system, named Sentinel, which aims to link many of these large databases as a resource that can be used for safety signal generation and observational epidemiological studies. In the UK, the Connecting for Health programme could provide similar information.

The databases described above contain patients' records of drug exposure and records of outcome in the same database. This information can also be held in separate databases that include unique identifiers to enable an individual's records in more than one database to be linked. Patient-identifiable information is not available. However, the unique code of these databases means that, for example, information from hospital visits can be linked with that from primary care. It also means that when a patient changes their doctor, the historical records are easily available.

Two examples of such systems are the Medicines Monitoring Unit (MEMO) system based in Tayside, UK, and the Pharmo system based in the Netherlands. The MEMO system uses separate databases of encashed

Box 1 | **Spontaneous reporting systems**

Advantages
- Can be used throughout the life cycle of a drug
- Can be used for generation of safety signals
- Can be used to identify rare adverse effects
- Can be used by all stakeholders

Disadvantages
- Under-reporting of adverse events
- Can produce reporting bias
- Variable quality of reports
- Captures mainly short-latency events
- Cannot be used to calculate frequency of events

prescriptions, primary-care information and hospital discharge records, which are linked through a unique identifier. The Pharmo system links community pharmacy data and hospital data within well established hospital catchment areas, and has been extended to include primary-care data and ~500,000 patients. It has proved to be a powerful tool for conducting follow-up studies and case–control studies for evaluating drug-related adverse effects. One of the most important of these studies assessed the possible association between Ca^{2+} channel antagonists and cancer[7].

Prescription event monitoring (PEM) is another approach to using patients' medical records to study drug safety. Prescriptions obtained from the UK Prescription Pricing Authority are used to create cohorts of patients who are exposed to new drugs, and event data are subsequently collected from general practitioners who prescribe these drugs. The methodology is transferable to other situations, and PEM has been shown to be feasible and useful in Japan and New Zealand[8].

The databases described above provide a relatively cheap and efficient source of information for studies of drug safety. However, it is important to note that the data in these databases are not usually collected for pharmacoepidemiological purposes, and as such the data may have limitations. For example, many databases do not include data on socio-economic factors, and some key variables such as smoking status, body weight or usage of over the counter medicines, may be erratically recorded. Furthermore, databases generally record which prescriptions are issued or dispensed, rather than information on patient exposure to the drug.

In addition, although pharmacoepidemiological studies provide more reliable information than that obtained from passive reporting and are a mainstay of active post-marketing safety surveillance, such studies have their limitations. The lack of randomization means that the risks of bias and 'confounding' need to be carefully considered when interpreting the results. Confounding by indication occurs when the safety issue that is studied (for example, an increased risk of bronchospasm with a bronchodilator drug could be related to the reason for prescribing the drug (in this example, asthma) and not the drug itself, and is particularly difficult to control for. Another limitation is that new drugs are often initially used in patients with more refractory disease, who may be at greater risk of adverse effects owing to multiple concomitant medications and the poorly controlled disease process.

Clinical trials. Controlled clinical trials that have a primary end point of safety can be important tools for active surveillance, because randomization of subjects should allow associations to be interpreted as causal. Such clinical studies require considerably more patients and are usually of longer duration than trials that have been established for licensing purposes. However, large trials that have been established to address safety may be less labour intensive than licensing trials.

This is well illustrated by the large simple trial to address the safety of antipyretic drugs in children who are <2 years old. This practitioner-based study compared the rate of hospitalization due to severe harm among children who were given ibuprofen or acetaminophen (paracetamol) to control fever[9]. Approximately 20,000 children with a fever were randomized, and no difference was found in the rates of hospitalization owing to specific safety end points (acute gastrointestinal bleeding, acute renal failure and anaphylaxis). Where possible, studies to evaluate the risk of treatment should be simplified by reducing data collection to a minimum. Such trials are especially useful when a single question is being asked.

Using the pharmacovigilance tool kit

TABLE 1 identifies some key study designs that could be used to investigate safety issues or study the safety profile of a drug following marketing authorization. Factors that should be taken into account include the nature of the required information, the reason for conducting the study, the estimated exposure of the patients to the drug and the main location of prescribing.

This table is not exhaustive but provides a starting point for considering how best to obtain the required information. The following three examples of current post-marketing investigations of adverse events associated with new medicines illustrate how various approaches are being integrated. They also indicate how a tool kit for pharmacovigilance investigations might be constructed using different methodologies to address specific situations.

Data collection on adverse reactions to HIV drugs (DAD study group). This is an ongoing series of observational studies in over 30,000 patients from established cohorts of patients who are HIV-positive. Its initial purpose was to investigate the possible association between the use of antiretroviral drug therapy (ART), the stage of HIV disease, cardiovascular risk factors and the incidence of stroke and myocardial infarction[10]. Associations between the duration of ART, the nature of the therapy used and the incidence of myocardial infarction were identified. Furthermore, some forms of ART were found to increase the risk factors for cardiovascular disease. There are plans to extend the remit of the DAD group to other long-term safety issues that are associated with ART.

These studies illustrate the use of condition-specific registers in observational studies on the effects of different forms of therapy, using safety as an end point. However, owing to the observational nature of the studies, results can only be presented as associations and inferences on causality cannot be made.

Table 1 | **Key study designs for various pharmacovigilance situations**

Estimated exposure of patient to drug	Primary-care exposure	Safety concern identified	Missing data	Tools
High	Yes	Yes	No	LST and observational studies (including PEM)
High	Yes	No	Yes	Observational studies
High	No	Yes	No	LST and registry (drug or disease)
High	No	No	Yes	Registry (disease)
Low	Yes	Yes	No	Observational studies (including PEM)
Low	Yes	No	Yes	Observational studies (including PEM)
Low	No	Yes	No	Registry (drug or disease)
Low	No	No	Yes	Registry (drug or disease)

LST, large simple trial; PEM, prescription event monitoring.

Human papilloma virus vaccine. High-risk human papilloma virus (HPV) types can be found in 99% of cervical cancers. Cervarix (GlaxoSmithKline) is a vaccine against HPV, and a routine immunization programme in UK females from the age of 12 or 13 years was started in September 2008. The UK is one of the first countries to undertake such a programme, and it is clearly important to define both the safety profile of the vaccine in real time, as well as its long-term efficacy.

The safety programme comprises three components. The first is the daily assessment and categorization of all new reports from the Yellow Card Scheme, with consideration of the cumulative data for continuous signal generation purposes. The second component is an 'observed versus expected' analysis of key adverse effects of interest, which is a form of active surveillance and can be used to assess causality in a universal immunization programme for which an unbiased control group cannot be obtained. Data are also being obtained from the GPRD to determine the background rates of outcomes of interest. The third component is a post-authorization clinical trial to investigate the risk of autoimmune diseases following vaccination.

The safety programme is accompanied by a communication plan, which includes the weekly publication of an analysis of adverse reactions that have been reported. By July 2009, 2,195 reports were received, or 157 reports per 100,000 administered doses of the vaccine.

Bosentan patient database. An example of active surveillance of a drug that has the potential to cause severe harm is provided by the database for bosentan (Tracleer; Actelion)[11]. This drug acts as a competitive antagonist of the neurohormone endothelin 1 by binding to both endothelin receptor subtypes. Bosentan was licensed for the treatment of adults and children with pulmonary arterial hypertension, in whom it has been shown to increase exercise capacity. Bosentan may cause liver damage; it is also a teratogen and therefore should not be used in females of childbearing potential without appropriate contraceptive precautions. It interacts with many drugs, especially cyclosporine and oral hypoglycaemic drugs, by altering their metabolism.

Specialist hospital centres that prescribed bosentan maintained disease registers of patients with pulmonary arterial hypertension as part of a patient access programme. Patients receiving bosentan were contacted every month by the distributors of the drug to check that they had undergone liver function tests and, in females of childbearing potential, a pregnancy test. Failure to comply, or doubt about the results of the tests, triggered referral back to the clinician.

Future directions in pharmacovigilance

As the pressure for earlier access to new medicines increases, the use of appropriate methodologies to investigate their safety is vital. Complementary and integrated methods need to be optimally used, and there is a need to develop the capabilities for real-time safety monitoring.

Additions to the pharmacovigilance tool kit may relate to the increasing use of personalized medicines. The use of pharmacogenetics to test for genetic variants that are known to increase the risk of adverse effects — such as the human leukocyte antigen (HLA)-B*5701 haplotype, which may predict the risk of hypersensitivity reactions to the ART abacavir (Ziagen; GlaxoSmithKline)[12] — needs to be further developed. Among the other techniques that are currently being studied is the more formalized use of quantified benefit/risk modelling[13–15]. One of the merits of such an approach is that all parties involved in assessing new drugs can be involved — the sponsor, the regulator and the patient. There is a pressing need to evaluate these evolving techniques in real-life drug safety scenarios.

In summary, integrating evidence from a carefully selected range of sources, and understanding their strengths and limitations, rather than striving to move up a 'hierarchy' of evidence away from less robust data, offers the greatest hope of meeting the challenges of pharmacovigilance.

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doi:10.1038/nrd3002
Published online 18 September 2009

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