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Challenges in ensuring drug safety

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ABSTRACT Recent high profile cases have highlighted the importance of establishing the appropriate balance of benefits and risks regarding drug therapy. The regulatory authorities and the pharmaceutical industry are responsible for ensuring drug safety, but prescribers and patients also have responsibilities in this regard. Providing better education for professionals and developing better information for patients are amongst the most important challenges to be faced.

KEYWORDS Communication, conflict of interest, drug regulation, drug safety, education, pharmacoepidemiology

LIST OF ABBREVIATIONS Association of the British Pharmaceutical Industry (ABPI), Centres for Education and Research in Therapeutics (CERTs), European Medicines Agency (EMEA), General Practice Research Database (GPRD), Medicines and Healthcare products Regulatory Agency (MHRA), non-steroidal anti-inflammatory drug (NSAID), selective serotonin reuptake inhibitor (SSRI)

DECLARATION OF INTERESTS K Beard is a member of Expert Advisory Groups of the Commission on Human Medicines, and of the Pharmacovigilance Working Party of the Committee on Human Medicinal Products in Europe. P Waller was formerly employed by the UK regulatory authority and currently holds a consultant contract with the Medicines and Healthcare products Regulatory Agency. Views expressed here are personal and do not reflect the views of any other group.

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INTRODUCTION

Concern about drug safety has gained a high profile in the recent past, and several issues have served to exemplify this. The publicity, controversy and possible lasting damage to public health done by the MMR vaccine incident rumbles on. Other prominent and recent examples have included rofecoxib (Vioxx), marketed in 1999 and withdrawn from use in 2004 amid concerns about cardiovascular safety, and the evolution of the risks and communication about suicidal ideation with SSRI antidepressants such as paroxetine (Seroxat). The 'Northwick Park incident', when healthy young subjects suffered unexpected and severe adverse effects during a phase I clinical trial, raised public awareness about safety of medicines in general, but is not directly relevant in the context of this discussion on post-authorisation safety of medicines.[1] The report of the House of Commons Health Select Committee in 2005 on the influence of the pharmaceutical industry has brought these, and many other aspects of the theme, into focus.[2] The rofecoxib story stimulated many to ask what are the key problems in assessing drug safety, why problems cannot be spotted sooner, and what can be done to prevent the same sort of thing happening again. Some aspects of this complex picture are discussed here:

- Science and regulation;
- communication;
- conflicts of interest;
- education and training.

PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY

Developing the science of pharmacovigilance, that is the detection, evaluation, understanding, and prevention of adverse drug reactions, is necessary because clinical trials cannot give us all the answers about safety at the time medicines are licensed. Those trials study too few patients to give all the answers we need, and the subjects that are studied are likely to be unrepresentative of, and healthier than, the general population likely to be treated. Most trials are also too brief to have any hope of detecting long-term side effects. The upshot of all this is that only side-effects that are common will be detected in clinical trials, so other methods are required once medicines are in regular clinical use.

Pharmacoepidemiology, the science of studying drug safety and use in the population, is a relatively young discipline but is recognised as an important tool for

promoting public health in relation to medicines. Spontaneous reporting of adverse reactions ('yellow cards' in the UK) is the system whereby health professionals, and now patients, can report to the regulatory authority their suspicions that a medicine may have caused a patient some harm. New methods of interrogating such data have evolved and these methods help in the early detection of 'signals' of possible safety problems. While there are clear limitations to these systems, many important safety signals have been detected over the years. Arguably, however, too much of the available resource is being channelled in this direction, and more emphasis needs to be given to the development of the data resources (e.g. large multipurpose databases) and observational research methodologies that are needed to investigate signals. In this way, a signal or suspicion that there may be a problem with a particular drug could be quickly tested in a robust scientific manner. This current imbalance of inputs between adverse reaction reporting systems and other methods could potentially be addressed by a single European reporting system. This would require investment but should be more efficient and economical, both for regulators and the pharmaceutical industry, than the present piecemeal arrangement.

Some progress is being made. Drug regulation in the post-authorisation period has recently embraced the concepts of risk management and pharmacovigilance planning. It is now a legal requirement for manufacturers that medicinal products newly licensed for human use in the EU must have in place a risk management plan. These plans must lay out what is and is not known about safety and how the manufacturer proposes to extend knowledge of safety as the product becomes more used. It is important that pharmacoepidemiologists become involved in supporting the pharmaceutical industry in planning and delivering on risk management. A real challenge lies ahead in the implementation of this legislation and in the deployment of sanctions should adequate standards fail to be met.

The cardiovascular safety of rofecoxib illustrated that problems may still emerge from clinical trials after a medicine has been authorised and used widely. The only time that the regulatory authority is routinely provided with all the available safety information from clinical trials is when the marketing authorisation application is made. The regulator may certainly make a specific request if concerns arise from other data, but while such data continue to be generated from trials in the post-authorisation period, they may only be submitted if the company perceives there to be a safety problem or applies for an extension to the authorisation. One important recent advance is that steps are being taken to make clinical trial data publicly available, but there is a need for ongoing systematic scrutiny of the entire safety data set for any given drug, that is independent of the manufacturer.

COMMUNICATION ABOUT DRUG SAFETY

When a major new story about drug safety breaks, patients and carers may be justifiably concerned and communication is a major challenge. Health professionals must now expect more knowledgeable patients, and need to develop a culture of openness, including the admission of ignorance when they do not know all the answers. Doctors and pharmacists receive vast numbers of communications from numerous sources. To help them sift and prioritise, it is important that drug safety communications from the pharmaceutical industry and from the regulatory authority should focus on what is truly important. Patients themselves, while having more potentially useful information available, are also exposed to information overload. Much of that information comes from the internet, and there is a major challenge in helping consumers distinguish the good from the bad, and the useful from the potentially harmful. Promotion of accredited or approved websites would be one way of tackling this.

Patients now have an opportunity to be involved more widely in the drug safety process, notably through the reporting of possible adverse reactions using yellow cards. Presently information about medicines (including side effects) comes from a variety of sources including the statutory patient information leaflet, patient support groups, leaflets (to be found in health centres, clinics or pharmacies) and other media (including the internet, the press and magazines). Perception of risk–benefit balance is a complex process, and it is important to remember the benefit part of the equation. For example, arthritis sufferers may well be happy to trade the risk of gastrointestinal or cardiovascular events in return for the effective pain relief afforded by NSAIDs. Patients clearly wish to be involved in that sort of decision-making, and need to be properly equipped to do so. Patient information leaflets are far from perfect, and this is under review. There is a plan for a complete redesign to make these readable and generally usable, and to include meaningful information about risk. Patient involvement by user-testing of leaflets in the development process is a recent new requirement under European law.

CONFLICTS OF INTEREST

Taken in the very broadest sense, conflicts of interest represent a significant, if not immediately obvious, challenge. Conflicts may occur at any point from discovery to consumption of medicines, and at any point in the assessment of safety.

The regulatory authority (the MHRA and ministers) has a conflict in wishing to encourage innovation in new medicines for patient benefit, whilst protecting public health by preventing exposure to unnecessary harm.[3] The MHRA must be clear about potential conflicts of interests among the agency's many advisors. The code of practice for that has recently been reviewed and is publicly available.[4]

Patient support groups may also have potential conflicts of interest. They are potentially valuable sources of support and information, but the recently revised ABPI Code of Practice requires openness in terms of any financial support that might have been given.[5]

Academics and health professionals may encounter conflicts of interest at various levels. In many organisations there now exist local arrangements and policies to deal with potential financial conflicts. Ideally, academic researchers would be well-informed, independent, accountable, honest and free to express their opinions, but there are many potential conflicts. In addition to pharmaceutical industry funding, sources of conflict might include the pressure to compete for research grants, and the pressure to publish and maintain a good research profile and reputation. Conflicts may persist into publication of results, although the system whereby clinical trials are now registered should help guard against the burying of potential safety problems in negative trials that never see the light of day. Any tendency to publish only positive findings may result in bias that distorts perceptions, and there have been suggestions that support from the pharmaceutical industry for research may exacerbate this. However, for practical and financial reasons, the suggestion that all clinical trials should be independent of industry funding is not a realistic option in the foreseeable future.

EDUCATION AND TRAINING

While the main responsibility for post-marketing drug safety lies with the regulatory authority and the pharmaceutical industry, it also depends crucially on prescribers. Much has been written on the drift away from formal clinical pharmacology teaching in the undergraduate medical curricula in the UK. The British Pharmacological Society has published a proposed curriculum that might redress that, but the current nature and style of undergraduate medical teaching does not lend itself well to the proposals. In the UK, a significant challenge is presented by the emergence of non-medical prescribers including nurses and pharmacists.

Clinical pharmacology and pharmaceutical medicine are recognised as postgraduate medical disciplines offering specialist training, and while many academic departments do offer postgraduate courses specifically in drug safety, the UK and Europe lag far behind North America in that regard. In the UK, the MHRA has now embarked on a determined effort to reach out and engage academia in the study of drug safety using all available data resources. This includes, but is not limited to, use of the now world famous multipurpose GPRD. In Europe, the EMEA is engaged in an exercise to construct a network of academic centres involved in the study of drug safety so that important questions can be addressed quickly, or even proactively. There are other good examples, for example the CERTs in the US, and many other national groups in Europe and further afield.

CONCLUSIONS

A model for the future conduct of pharmacovigilance was proposed in 2003.[6] This emphasised the need to acquire best evidence, to use that evidence for robust scientific decision making and to create better tools for the protection of public health. That three level axis must be informed by a culture of scientific development, and be supported by outcome measures and audit. There has since been some progress in developing the model in Europe and beyond, but many challenges remain.

KEYPOINTS

- Previously unsuspected toxicity, real and imagined, from drugs and vaccines has raised the profile of drug safety.
- Pharmacovigilance (detecting and preventing adverse drug reactions) and pharmacoepidemiology (safe drug use in populations) are primary methods for studying and improving drug safety.
- Effective communication about drug safety requires the availability of trusted valid information from many sources, including the medicines regulatory authorities and the pharmaceutical industry.
- Conflicts of interest for the pharmaceutical industry, regulatory bodies, patient groups and health professionals require careful consideration.
- Better education and training for health professionals, and better patient information, should help in the processes of balancing benefits and risks, and in making sensible treament choices.

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