The benefits of drug treatments, especially new ones, are the subject of much publicity both from advertisements and articles in scientific journals. The difficulties of prescribing receive much less attention except when disasters occur. The conference sought to redress this balance, and considered not only the detection and management of adverse effects of drugs but also other aspects of the healthcare process that contribute to safe prescribing.

Detecting and managing the adverse effects of drugs

Adverse effects are an inevitable consequence of the use of medicinal products and need to be managed actively, not ignored or wished away. The safe use of a drug requires an individualised risk/benefit analysis. In most cases, evidence showing the benefits of drug treatment is readily available. However, information on the risks or adverse effects is often limited to a bald list of adverse effects that have been reported during clinical trials.

Most of the information available on the adverse effects of a drug is based on individual case analysis. Before the drug is marketed, the information comes from clinical trials; after marketing, it comes from spontaneous reporting (eg yellow cards). Although huge resources are used by both drug developers and drug regulators in the collection and collation of this information, the case was put for alternative approaches to be considered. Individual case analysis is most useful for generating a signal that there may be a problem, but it yields little information about the incidence of the effect, or causality. For example, there are about 2,000 licensed drugs in the UK, and 4,000 preferred terms for adverse reactions. Of the 200,000 reactions reported to UK regulatory authorities in the past 11 years, 60% are the sole report of that event for that drug. Individual case analysis cannot be used to calculate the incidence of an adverse effect, nor can it be used to demonstrate the absence of a problem. There should be greater emphasis on meta-analysis of adverse effects, and use of data from patients in control groups to calculate the background rate of these effects. Some are more likely to be caused by drugs than others, so clinical pharmacologists should be involved in drug development to predict the spectrum of adverse effects that might be expected, and to design studies to investigate them. Drugs are licensed on the basis of causal benefit, but risk should be assessed on the basis of causal adverse effects.

A novel classification of adverse effects

A novel classification of adverse effects, comprised of the dose, the time course, and patient susceptibility, was proposed:

- **Dose** All adverse effects are related to dose, so greater emphasis on the dose-responsiveness of adverse as well as therapeutic effects during drug development could improve their safe use. If an adverse effect occurs at a higher concentration than that required for the therapeutic effect, this is called a *toxic* effect. Reducing the dose may eliminate the adverse effect while retaining the beneficial ones. If the adverse effect occurs at a similar concentration to that required for the therapeutic effect, it is called a *side effect*. These types of effect cannot easily be avoided by altering the dose. If the dose–response curve for an adverse effect lies at a concentration far below that required for the therapeutic effect, the patient could be described as *hypersusceptible* to the effect. The term ‘hypersensitivity’ is not used as this implies an immune basis for the effect, and not all such effects are mediated in this way.

- **The time course** Most reactions are time-dependent, and can be further divided according to when they usually occur. This ranges from immediate (eg red man syndrome after rapid infusion of vancomycin) to very delayed and even second-generation effects (eg vaginal adenocarcinoma in daughters of women given stilboestrol during pregnancy).

- **Patient susceptibility** Identification of the factors that influence this (eg age, gender, comorbid conditions) is an important part of drug development. Some of the most important susceptibility factors are pharmacogenetic differences between patients.

Pharmacogenetics

About 60% of drugs implicated in hospital admissions related to adverse drug reactions are metabolised in the liver by polymorphic cytochrome
P450 enzymes (CYP); this compares with 7–22% of randomly selected drugs. The distribution of variants can vary considerably with ethnicity and location; this must be taken into account when proposing alterations to a dosage regimen. A specific relationship between allelic variants and drug metabolism has been identified for some drugs (e.g. CYP 2C9 and warfarin), but many effects are polygenic and subject to large environmental influences. These factors, and the variability of the expertise to perform the tests, limit the clinical application of pharmacogenetic profiling. Even when a reliable test is available, it may not be deemed cost-effective on a national scale (e.g. factor V Leiden testing for women taking the oral contraceptive).

**Identifying patients at risk of adverse cardiac effects in clinical practice**

The effect of drugs on the electrocardiogram (ECG) cardiac output (QT) interval was used to illustrate some of the issues around the identification of patients at greatest risk of cardiac adverse effects. Some drugs (e.g. sotalol, quinidine, disopyramide) block the IKr potassium channel in cardiac tissue as part of their therapeutic action; these drugs prolong the QT interval, and are associated with a high risk of causing the potentially fatal arrhythmia Torsade de Pointe. Many other drugs (e.g. antipsychotic drugs) can block the voltage-gated potassium channel IKr, but the risk is much lower. However, because these drugs are so commonly prescribed the overall potential for doing harm is great. Prescribers want to identify patients at high risk of arrhythmia before prescribing the drug. A syndrome of prolonged QT interval is well recognised and easily identified on the ECG, but this represents only one end of a spectrum of ECG abnormalities. Many of the drugs that have the potential to prolong the QT interval are prescribed by specialists (e.g. psychiatrists) for whom detailed analysis of the ECG for subtle QT changes is not part of routine practice. The use of patient-held QT cards to alert other prescribers could improve the risk from these drugs.

Using hepatotoxicity as an example, Professor Neuberger considered the challenges facing prescribers once an adverse effect has been identified. Despite the myriad functions of the liver, methods of detecting liver abnormalities are largely limited to the measurement of ‘liver function tests’, most of which are markers of liver damage rather than function. Interpretation of liver function tests is difficult: 10% of patient given isoniazid will develop a transaminitis, but it is transient. Liver biopsy yields more information but carries a small risk of serious harm, so it cannot be recommended for monitoring or investigating of minor abnormalities. Use of novel protein and metabolite markers from plasma and urine is some way off. Future analysis may focus more on trends rather than on absolute changes, for distinguishing minor changes from progressive potentially serious ones.

Dr Robin Ferner brought these considerations together with illustrations of several drugs that commonly cause harm. For example, warfarin is an effective anticoagulant but can cause bleeding. Careful analysis of the risks and benefits of this drug has changed the way it is used.Guidelines are available for the safe initiation of therapy, duration of therapy for various diseases, and advice on peri-operative anticoagulation. This sort of detailed information is almost never available when a new drug is marketed. Determining how best to use a medicine requires a culture that can learn from errors and failures.

**Safe prescribing within healthcare systems**

**Error management**

Safe prescribing is not just a function of the safety of the medicinal product itself. Prescribing takes places within a wider healthcare system, and the safety of this system can be as important as the characteristics of the drug itself.

Three types of error occur in healthcare systems:

- **Slips and lapses** are the simplest types of error. They are purposeful but incorrect responses, for example, writing 5 mg instead of 0.5 mg. These types of error are more common when prescribers are tired or distracted. Their impact can be minimised by appropriate checking and scrutiny of prescriptions.

- **Mistakes** are rule-based errors: they can involve the incorrect application of a ‘good’ rule, or the application of a ‘bad’ rule. An example would be the use of an incorrect formula to adjust the dose of a renally excreted drug.

**Conference programme**

- **Detecting an adverse drug reaction**
  Professor Stephen Evans, London School of Hygiene and Tropical Medicine

- **Classifying adverse drug reactions**
  Dr Jeffrey Aronson, University of Oxford

- **The genetics of adverse drug reactions**
  Professor Munir Pirmohamed, University of Liverpool

- **Adverse drug reactions and the liver**
  Professor James Neuberger, Queen Elizabeth Hospital, Birmingham

- **Adverse drug reactions and the heart**
  Professor John Camm, St George’s Hospital Medical School, London

- **Managing human error**
  Professor James Reason, University of Manchester

- **What to do when things go wrong**
  Professor Kent Woods, University of Leicester

- **Cure or kill: commonly prescribed poisons**
  Dr Robin Ferner

- **Was it murder?**
  Professor Robert Forrest, University of Sheffield

- **How steroids turn you on (and off)**
  Professor Rod Flower, William Harvey Research Institute, London
Knowledge-based errors result from uncertainty. When faced with an unfamiliar situation, we rely on experience and other algorithms to determine a course of action. This type of activity is especially error-prone. Analysis of several medical disasters has shown that similar situations produce similar errors, even though the people involved are different. These types of error challenge us to change the systems within which we work, and to improve training. It is important to recognize that the final error in the chain results in the harm, but the other contributory factors are of equal importance, and must be addressed. Ninety percent of errors are not culpable; healthcare systems must learn from this to reduce the risk of harm to future patients.

**Error management in the NHS**

Professor Kent Woods spoke about the need to change the culture of the NHS from one of ‘blame and shame’ to one of safety and constant vigilance. *An organization with a memory*, written by the Chief Medical Officer in 2000, focused on the need to identify, learn from, and disseminate the lessons from systems failures. The report made several specific recommendations, one of which was to reduce by 40% the number of serious errors in the use of prescribed drugs by 2005. Systems improvements have an important part to play in this, but many of these types of error result from a lack of knowledge. Most prescribing in hospital is done by those most inexperienced and most likely to make errors.

The Chief Medical Officer recommended in April 2001 that medical school curricula should include drug safety. Some of the barriers to the implementation of this are the organisational complexity of the design of curricula, and the reduction in numbers of academics in specialties such as clinical pharmacology. Large, new cohorts of non-doctor prescribers will also need this support and training. Prescribing, like any skill, is associated with a learning curve; systems are in place to deal with this in surgical training, it is imperative that systems are also developed to support new prescribers. Several resources are available including a core curriculum produced by the British Pharmacological Society. This is an area where innovative case-based and web-based learning resources could be useful to prescribers of all levels of experience, but these need adequate infrastructure support and regular updating.

**Deliberate misuse of prescription medicines**

Not all perils of prescription medicine are the result of inadvertent error: healthcare workers have used their access to prescription medicines to harm and even murder those in their care. These actions can be easy to conceal, so part of the safety culture must include systems to allow the reporting and prompt investigation of suspicious actions.

**References**

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5. Available on the British Pharmacology Society website. [http://www.bps.ac.uk/BPS.html](http://www.bps.ac.uk/BPS.html)