Detection, verification, and quantification of adverse drug reactions

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people in developed countries consume about 35% of their energy as fat, about 10 g/day of salt, and about 0.2 mg/day of folate, and nearly everyone is exposed to the risks of road injuries.

The chief merit of the increasingly popular convenience foods is their convenience. Individuals have little influence over their composition. Even foods that are described as being healthy can be high in sugar and salt, counterbalancing any benefit from added micronutrients, such as folic acid. But discouraging the use of convenience foods is not practical; we need collective action to reduce the amounts of salt, sugar, and saturated fat in foods, and a sensible policy on portion sizes in restaurants.

Of course, individuals have some choice, but for most people safety and health are minor determinants—value for money, convenience, and fashion rank much higher. Safety and health have to be part of the fabric of society, determined by experts with specialist knowledge, and translated into policies by governments, acting on our behalf. For years we have unquestioningly accepted the addition of iodide to table salt, to prevent thyroid disease; the prevention is silent. Charges of paternalism and pejorative labels such as "nanny state," with the false innuendo that we are being controlled against our wishes, are unhelpful because effective public health needs to be integrated into the infrastructure of society. We depend on governments and professionals to ensure that our lives are as healthy and as free as possible. Governments have the main responsibility and authority for maintaining public health, through education, regulation, legislation, and taxation. Not all decisions will be right, but it is not hard to ensure that most are and, given new knowledge, to correct those that are not.

An advisory role is not enough. Public health in countries such as Britain needs a stronger executive role, relatively free of short term political considerations. Watching our children (and ourselves) becoming overweight and claiming that it is all about choice is a denial of everything that public health and preventive medicine is about, and a denial of what makes a society civilised and worth belonging to. Public health and individual choice can flourish together, but the former should not be driven by the latter.

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The current system of verifying and quantifying adverse reactions to new drugs is too disparate. Epidemiological studies for testing a hypothesis have a part to play in protecting the public from the harmful effects of new drugs

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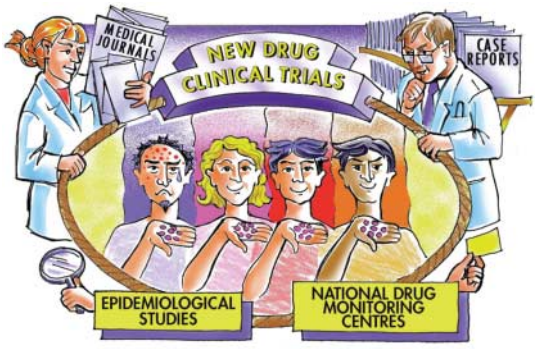
Although some will question the use of the term experiment on formal grounds, most experts will likely agree that the widespread marketing of a new drug is in fact a large experiment on a population. This is especially the case when it concerns a novel molecular entity with potentially a new set of clinical experiences. As the marketing of new drugs includes the discovery of adverse effects, the public's health would be best protected by a complementary set of techniques for the detection, verification, and quantification of safety issues. Yet the current approach to this is scattered and disappointing. We discuss why healthcare professionals are not aware of all safety problems of a drug at its introduction and why pharmacoepidemiology should complement the indispensable observational method of case reporting.

Sources and selection criteria

Our review is based on a search of PubMed using the terms adverse effect, adverse reaction, ADR, adverse event, adverse reaction monitoring, pharmacovigilance, cohort study, and case-control study. This yielded several thousand papers from which we excluded individual case reports and case series. From a list of cohort and case-control studies, we picked some recent examples of pharmacoepidemiological studies of adverse events with databases. We used the references from 50 of the most recent reviews, to gather the most important papers on this subject.



SUE SHARPLES

Limitations of clinical trials

Before drugs are marketed, they are extensively tested in animals and in clinical trials in humans. These tests tell much about the drug's efficacy but for several reasons relatively little about safety (box).

P+ *Systems for drug safety research and references w1-w10 are on bmj.com*

Good economical reasons preclude an endless quest for research before drugs are registered. Such research would make the development of drugs expensive, a price that ultimately is paid by the consumer.[1] More effort therefore should be put into researching the safety of drugs after marketing, especially in the evidence-free zone when drugs are first launched.[2]

Protecting society against the adverse effects of drugs requires early detection, valid verification, and quantification, which include assessing the frequency and severity of adverse events, dose relations, the time course, and susceptibility factors.[3]

In daily practice many signals of a potential adverse event are not followed by a systematic process of verification and quantification. One reason for this may be the transitional period between the signal of a problem and its confirmation. At this point every sensible professional response is open to discussion. If the problem is highlighted by a single case report, attention may fade; even if similar signals are produced by other case reports, the likelihood of a causal relation is often just debated unless more evidence emerges. Subsequent well designed epidemiological studies may provide additional verification. They also fulfil the need for quantification of the adverse effect. Whether such studies are performed usually depends on the initiatives of scientific groups with an interest in the topic. Another reason why safety issues may not be pursued systematically is related to who has the responsibility. Formally, liability rests with the pharmaceutical company, which acts as marketing authorisation holder, but as it does not have an economic interest in detecting safety issues it may lack incentive to investigate problems. Additionally, many problems related to a drug are caused by class effects, such as extrapyramidal effects due to neuroleptics. Then it is not always possible to blame a particular product or company. Drug authorities should take responsibility to safeguard public health in such a situation.

Adverse drug reactions

Detection

Adverse effects cannot be detected without astute professional observers. Case reports are among the most important tools for observational research.[4] All people exposed to a new drug comprise the potential catchment population for adverse effects. In a country such as the United Kingdom, with some 60 million inhabitants, a 1% cumulative exposure to a drug yearly would equate to 600 000 people using the drug at any time during that year. A rare adverse effect with an incidence of 1 in 10 000 might be detected in such a population, particularly when the adverse effect has a low background incidence, making it easily recognised. In the case of phocomelia due to thalidomide, for instance, recognition should have been easy but because of the unfamiliarity with drug safety problems at that time it took several years to identify a causal relation.[5] When an adverse effect is non-specific and has an appreciable background incidence, detection is more difficult. Similarly, it may be difficult to detect an adverse effect that is indistinguishable from the disease being treated—for example, arrhythmia as an adverse effect of antiarrhythmics. Such adverse effects may therefore remain unnoticed. One of the most common reasons for withdrawal of drugs from the market is hepatitis, which has a high background incidence making it potentially difficult to determine a causal relation.[6]

Limitations of most clinical trials in highlighting a drug's safety

Homogeneous populations
Most trials assess relatively healthy patients with only one disease and mostly exclude specific groups such as pregnant women, children, and elderly people

Sample size
Small sample size (up to 1000 patients) reduces the chance of finding rare adverse effects

Limited duration
Trials of short duration preclude the discovery of long term consequences such as cancer

Inability to predict the real world
Drug interactions can be substantial in a population as patients may take drugs concomitantly, a situation that can almost never be predicted from clinical trials

Voluntary reporting

Despite these problems in detecting genuine adverse effects, voluntary reporting of adverse reactions by clinical observers is inexpensive and effective. Basically, there are two systems. The first is a virtual one and relates to all correspondence and short reports in the medical literature. The second consists of national and international adverse drug reaction monitoring centres.

The medical literature

The medical literature is probably by far the most effective system for initial detection because case reports are detailed, assessed for quality by reviewers, mostly independent from commercial incentives, and open to interested parties. The collaborative output of the 20 largest medical journals in highlighting a new problem by a single case report easily outclasses every other system. Fourteen of 18 important adverse drug reactions were shown to be detected and verified by voluntary reporting, mostly through the literature.[7] Of 47 anecdotal reports published in 1963 in four major general medical journals, 35 were clearly correct, which seems to be satisfactory.[8] Not all published case reports represent genuine adverse reactions as there is always the risk of false positive signals.[8] Despite this, the medical literature is a highly efficient warning system for new adverse reactions, and often recognises rare events and people at high risk.[9 10]

Monitoring centres

The second system comprises national adverse drug reaction monitoring centres and the WHO Collaborating Centre for International Drug Monitoring. These are not open to third parties such as consumers, patients, and healthcare professionals. Most of these systems work with a yellow card scheme, which can be productive if active and well qualified staff considers the detection of adverse reactions as its primary objective. Such monitoring centres are,

Databases used by pharmacoepidemiological studies to test hypotheses. Values are relative risks (95% confidence intervals) unless stated otherwise

Study	Database	Drug	Adverse effect	Risk; comparator
Garcia Rodriguez et al[w1]	General Practice Research Database	Amoxicillin-clavulanic acid	Hepatic injury	6.3 (3.2 to 12.7); amoxicillin alone
Jick et al[w2]	General Practice Research Database	Appetite suppressants	Cardiac valve regurgitation	Risk 35/10 000 users (16.4 to 76.2) of fenfluramine or dexfenfluramine compared with 0/10 000 non-users
Zornberg and Jick[w3]	General Practice Research Database	Antipsychotics	Idiopathic venous thromboembolism	7.1 (2.3 to 22.0); non-use
Meier et al[w4]	General Practice Research Database	Postmenopausal oestrogens	Systemic lupus erythematosus	2.8 (1.3 to 5.8); non-use
Van der Linden et al[w5]	General Practice Research Database	Fluoroquinolones	Achilles tendon rupture	4.3 (2.4 to 7.8); non-use
Derby et al[w6]	General Practice Research Database	Flucloxacillin	Cholestatic hepatitis	Risk 7.6/100 000 users (3.6 to 13.9) as against 2.1/100 000 users of oxytetracycline
Straus et al[w7]	Integrated Primary Care Information Project	Antipsychotics	Sudden cardiac death	3.3 (1.8 to 6.2); non-use
Herings et al[w8]	Pharmaco-morbiditeitskoppeling	Angiotensin converting enzyme inhibitors	Hypoglycaemia	2.8 (1.4 to 5.7); non-use
Ray et al[w9]	Tennessee Medicaid	Benzodiazepines	Nocturnal falls	3.0 (2.3 to 3.8); non-use
Ray et al[w10]	Tennessee Medicaid	Tricyclic antidepressants (>300 mg daily)	Sudden cardiac death	2.5 (1.04 to 6.1); non-use

however, often understaffed, work in isolated non-academic environments, have all kinds of responsibilities for regulation, and are overwhelmed by reports from the pharmaceutical industry. Consequently there is little time for analysing the reports on adverse reactions sent in by doctors. The legal requirements for reporting adverse events to the Food and Drug Administration and European Medicines Evaluation Agency result in vast numbers of reports, all of which have to be processed. Many of these have a low likelihood of a causal relation. When it is likely that the literature produces really new signals in which more than 50% are causally related, most accounts of the systems that accumulate reports from industry consist of either known adverse reactions or unrelated adverse events. Considering the enormous investment in human resources in industry and government to run this system, efficiency is low. As in the end the cost will inevitably be paid by health insurance systems and patients, the price of drugs will further increase in the future.

Hypothesis generating signals

Over the past 30 years attempts have been made to enhance the recognition of adverse effects by "data dredging" or "data mining." The contribution of such techniques to detecting adverse reactions has been modest. When substantial numbers of reports are available, however, comparing the proportion of reports of an adverse effect with similar drugs may provide strong hypothesis generating signals, such as for rhabdomyolysis associated with cerivastatin.[11] Such comparison may even facilitate some sort of hypothesis testing relative risk assessment.[12 13] The validity of such techniques, however, is probably much lower than that of formal designs of epidemiological studies.

The originally embraced technique of prescription event monitoring has proved more difficult than expected.[14] Use of research databases such as the General Practice Research Database for the detection of adverse effects by generating an hypothesis has had only limited success. It seems better to restrict the use of such databases to hypothesis-testing epidemiological studies.

Verification and quantification

As soon as an adverse reaction is signalled, a hypothesis is raised that requires formal testing. Relevant questions are how often the adverse reaction occurs and how many times the risk of the adverse effect is increased by the drug.

To this end the observational designs of the cohort study and the case-control study have proved useful.[15] Cohort studies are particularly useful for uncommonly used drugs but are less useful if the disease being assessed is rare. Case-control studies are efficient for studying rare diseases but require that the drug is commonly used. An example of a successful case-control study was the determination of an association between vaginal carcinoma of the female offspring of women who had been treated with diethylstilbestrol during pregnancy.[16] The authors were able to show the association with only eight cases and 40 controls.

Summary points

More effort should be put into researching the safety of drugs after marketing

In daily practice many signals of a potential adverse event are not followed by a systematic process of verification and quantification

The medical literature is probably by far the most effective system for initial detection of adverse reactions to drugs

The current emphasis on the costly procedures of mandatory reporting should shift towards epidemiological studies for testing a hypothesis

Well designed cohort or case-control studies can adequately deal with bias and confounding, the two potential criticisms of these study designs. The issue of confounding by indication is seldom a problem with rare adverse effects because such unpredictable effects are usually not associated with the indication for treatment.[17] Although in such studies confounding by contraindication may play a part, it leads to a conservative estimate rather than to an overestimation of the true risk.[18]

The cohort and case-control designs can be used to test hypotheses in de novo field studies. Several databases facilitate the performance of such studies with prospectively gathered information on exposure to a drug and disease (see bmj.com). With these data resources, several successful pharmacoepidemiological studies have been performed (table). Unfortunately and despite the enormous growth of pharmacoepidemiology and its capabilities, most drugs are withdrawn on the bases of case reports and case series alone.[6] Therefore it is time these databases are used more consistently for hypothesis testing in research concerning drug safety.

In conclusion, society has the right to be safeguarded against the adverse effects of new drugs. The current emphasis on the costly procedures of mandatory reporting should perhaps shift towards epidemiological studies for testing a hypothesis. When particular drug classes and clusters of disease are involved, regulatory authorities and drug inspectorates should take the lead to fulfil their primary task of guaranteeing safe health care.

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Making decisions about benefits and harms of medicines

Trisha Greenhalgh, Olga Kostopoulou, Clare Harries

Even when good scientific data are available, people's interpretation of risks and benefits will differ

Drug regulatory authorities, such as the Medicines and Healthcare Products Regulatory Agency in the United Kingdom and the Food and Drug Administration in the United States, award product licences by assessing the balance between benefit and harm. The decision to revoke a licence generally hangs on evidence of lack of efficacy or risk of serious adverse effects, taking account of the seriousness of the condition and the range of other treatments available.

The authorities work at the level of the whole population. But individual patients may believe (rightly in some cases) that a particular regulatory decision is not in their own best interests, and vociferous campaigns sometimes result (box 1). Involvement of patients can be a powerful driver for improving services.[5] But both lay people and professionals are susceptible to several biases when making health related decisions (box 2). What can be done to ensure that the care of individual patients is not compromised by regulatory decisions intended to protect the population as a whole, and to encourage objective and dispassionate decision making in the face of cognitive biases?

Sources and selection criteria

This article was constructed through multidisciplinary dialogue between an academic general practitioner with a keen interest in evidence based and narrative based decision making, two cognitive psychologists specialising in risk perception, and an editor with a background in medical pharmacology. The authors drew on their own disciplinary perspective, expertise, and archives. The goal was not to produce an exhaustive overview of any of our areas of expertise but to use insights from one discipline (psychology) to illuminate findings from another (drug regulatory decisions).

P+ *Two more boxes and further references (w1-w17) are available on bmj.com*

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