people. Fourthly, the EU Clinical Trials Directive specifically addresses pharmacovigilance, and this should contribute to improvements in reporting in European clinical trials.⁹ Fifthly, although research databases have had a major impact on drug safety issues in recent years,¹¹ they have limitations, including limited power to detect rare events, and they focus on one area of the healthcare system. The announcement of the information technology strategy for the NHS could, if set up to do so, lead to the development of an integrated drug safety database, with enormous potential for earlier detection of adverse drug reactions.

Finally, sharing of data by prescribers, researchers, regulators, and the industry is essential. Legislation to protect personal privacy has been introduced in many countries; although important, it must not deter sharing of information that is needed to protect public health. Inability to share information because of legislation has already had adverse consequences—for example, in the criminal justice system.¹² Information also needs to be available to the general public, the consumers of medicinal products. However, this requires safeguards so that the data are appropriately interpreted, taking into account both harms and benefits of the drug. Without such safeguards, we may

face problems similar to the controversy concerning the measles, mumps, and rubella (MMR) vaccine, where an inappropriate focus on potential (and unproved) harms has generated mistrust and led to a decline in public health.¹⁰ To this end, appropriate strategies to communicate risk to the public are going to be essential.¹¹

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Assessing the benefit-harm balance at the bedside

We need pragmatic ways of using the best available information

As prescribers, we all aspire towards the goal of providing safe and effective medicines for our patients. At the bedside, we are routinely confronted with the challenge of determining which treatment (if any) offers the most appropriate tradeoff between benefit and harm. In ideal circumstances, we would base this assessment on the findings of a systematic review. But the reality is that systematic reviews and randomised controlled trials tend to focus on efficacy and seldom pay much attention to adverse effects.^{1 2} In contrast, product datasheets and drug reference texts (such as the *British National Formulary*) are laden with comprehensive lists of adverse effects. Is there really any need to look beyond these ubiquitous, easily accessible sources of safety data?

However, all is not what it seems. Lists of adverse effects can be extremely lengthy—for example, Bracchi noted 54 adverse effects for fluoxetine—and incorporating them into a useful analysis of the benefit:harm balance seems impossible.³ More recently, a member of

the British public wrote to the national press in bewilderment after discovering that his medication had more than 80 potential adverse effects.⁴ The threat of so many adverse effects seemed to swamp the prospect of benefit, and it comes as no surprise that the patient regarded the cure to be worse than the ailment.

A lack of quantitative information on the likelihood of occurrence complicates the problem further. Bracchi attempted to get round this by requesting frequency data from drug manufacturers, but only one of the 120 companies contacted was able to help.³ In an attempt to improve product datasheets, European regulatory authorities have proposed the use of qualitative terms such as “common” to “very rare.” Research has shown, however, that these terms lack precision and are not as well understood as numerical data.⁵

An additional table showing scenarios for which treatment decisions should be based on a detailed evaluation of the benefit to harm balance is on bmj.com

Bedside scenarios in which treatment decisions should be based on a detailed evaluation of the benefit to harm balance

A. When there is a narrow margin between benefit and harm

A1. Treatment is of modest or uncertain benefit, with some possibility of harm	Aspirin for primary prevention of cardiovascular events in a healthy patient, bearing in mind the increase in gastrointestinal haemorrhage
A2. Treatment has considerable potential for benefit, but there are major safety concerns	Aspirin for a patient with a stroke, but who has a history of gastrointestinal haemorrhage

B. When there is more than one efficacious treatment with differing safety profiles

B1. Treatments are of equivalent efficacy, but one agent may have a better safety profile	Selective cyclo-oxygenase-2 (COX-2) inhibitors rather than conventional non-steroidal analgesics in reducing the risk of gastrointestinal ulcer complications
B2. Relative benefits and harms differ substantially among the available treatments—for example, the most efficacious drug may have serious adverse effects, whereas the least effective agent is safer	Warfarin or aspirin in a healthy middle aged man with lone atrial fibrillation

Furthermore, we need to take into account the strength or quality of the evidence in assessing the best treatment for a patient. Adverse effects data from a high quality study should have a greater role in the treatment decision than uncorroborated anecdotes. However, the provenance of the safety information in datasheets and reference texts is not always known, and it can be very difficult to determine how real a particular threat is. Prescribers are therefore forced to grapple with the curious conundrum that quantitative efficacy data from a high quality systematic review have to be weighed up against adverse effects data of uncertain origin and indeterminate frequency.

It would clearly be impractical to carry out exhaustive safety analyses for every treatment decision. Instead we should focus on recognising the specific occasions (table, and see bmj.com) on which we need to look beyond datasheets and reference texts. As an example, most prescribers would think twice before recommending aspirin in either of the first two scenarios in the table. Do the cardiovascular benefits outweigh the gastrointestinal harms?

This question can be addressed in an evidence based manner by using the method of Glasziou and Irwig to estimate the absolute benefit and harm according to the patient's risk profile.⁶ Here, the reduction in cardiovascular events and associated increase in gastrointestinal haemorrhages is calculated by using data from systematic reviews and observational studies of aspirin therapy.⁷ The benefit:harm tradeoff across a range of risk levels can then be summarised graphically to help bedside prescribers decide whether aspirin therapy is warranted or not.

Precise estimates of harm are important when the available drugs have equal efficacy but there are potentially valuable differences in the rates of adverse effect—for example, when deciding between a selective cyclo-oxygenase 2 inhibitor and another analgesic (table). The treatment decision here may hinge on which agent offers the more attractive safety profile. While single trials may not have sufficient power to distinguish adequately between the drugs, a meta-analysis may show small but significant differences in complication rates of ulcers.⁸

The therapeutic challenge in the listed scenarios lies not in the recognition of new adverse reactions, but in having enough data to guide the management of

well established safety concerns. Drug safety researchers must now move beyond their traditional focus on the detection of adverse reactions and face the new hurdles of characterising known reactions in greater detail. After all, Bottiger argues that most deaths related to adverse reactions are not from rare, new, or unexpected complications but are due to well recognised reactions.⁹ We would be able to manage these adverse reactions better if we had information on their frequency, dose responsiveness, time course, and patients' susceptibility factors.¹⁰ Most importantly, we also need to ensure that safety evaluations are based on data that are of the same high standards required in the assessment of therapeutic efficacy.

Are these realistic goals? Probably yes, says Vandenbroucke in this issue (p 2), but only if we can remove the dogmatism that prevents a happy union between evidence based medicine and traditional pharmacovigilance.¹¹ In making the best treatment decisions for our patients, it is time that we tackled the weaknesses of the existing data and moved the science of drug safety forward.

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