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The road to health care

Balancing benefits and harms of interventions is essential

"There are some patients that we cannot help; there are none whom we cannot harm."

Attributed to Arthur L Bloomfield

Before you next get into your car or walk out into the street, reflect that the number of deaths from road crashes in the United Kingdom is about 3400 a year.[1] Elsewhere in the world the rates are up to six times higher.[2] Now compare that with the extrapolated figure for the United Kingdom of more than twice that number of deaths each year from adverse drug reactions, estimated from the results of a prospective study published in this theme issue of the *BMJ*.[3] Now try to estimate the benefit to harm balance of a road trip and the benefit to harm balance of a drug that you have recently used.

But drugs are far from being the only interventions we use in health care; even when drugs are prescribed they are often only part of an overall plan of care. Other interventions include lifestyle changes, surgery, physiotherapy, radiotherapy, rest, and a panoply of other interventions that may be recommended by medical and paramedical staff, relatives and friends, practitioners of complementary and alternative medicine, and the latest issue of *Cosmopolitan* magazine.

Even with drug treatments we often lack the necessary information to estimate the balance between benefits and harms. Randomised trials are primarily concerned with addressing uncertainties about potential benefits and seldom focus on safety issues. Moreover, even when information about safety is collected, the data may be sparse, may not be collected systematically, and may not be comparable from study to study. This makes the benefit to harm balance difficult to assess.

Consider how much more challenging it is to assess the benefit to harm balance for non-drug interventions. Often such interventions are implemented without reliable evidence of their beneficial effects, let alone their harmful ones. For example, most evaluations of different prostheses in total hip replacement are uncontrolled, and a systematic review found that the primary evidence was too weak to draw valid conclusions.[4] Cryotherapy is widely used to treat warts, but evidence of its efficacy and safety rests on a handful of randomised controlled trials and is reportedly both limited and contradictory.[5] Wax softeners are used by the gallon, but we don't know about their relative effectiveness, let alone their safety.[6] Children with bronchiolitis are segregated in many hospitals to reduce the risk of nosocomial infection, but we do not know if this is effective.[7] And we are still unable to answer with certainty the age old question of which position women should adopt when delivering their babies.[8]

In some cases not only is there no evidence of benefit, but we may remain oblivious to the possibility of harm. How many times have you heard someone say that even if an untested treatment is not going to do any good it is unlikely to be harmful? But there are several examples of interventions that were confidently expected to be both beneficial and completely safe, expectations that were not fulfilled. For example, high concentrations of oxygen for premature babies, which caused retrolental fibroplasia[9]; bed rest for low back pain, which can delay recovery[10]; albumin for resuscitating critically ill patients with hypovolaemia, burns, or hypoalbuminaemia, which probably worsens outcomes[11]; and class I antiarrhythmic drugs, which unexpectedly increased mortality after myocardial infarction.[12] We banned relatives from accompanying women during delivery in many hospitals, only to learn decades later that this is far from ideal in most cases,[13] and we have implemented some guidelines on how to approach deliberate self harm without realising that they were often wasteful of resources if not actually harmful.[14]

In all areas of health care—in preventive medicine in both individuals and the population, in screening and diagnosis, in therapeutic interventions (whether drugs are used or not), and in monitoring treatment—we need information about all the effects, both beneficial and harmful, of the relevant interventions, effective ways of gathering that information, proper reporting and effective indexing in databases, and analysis and integration of all this information. And we need people from different disciplines to work together to obtain it. Armed in this way, healthcare professionals should be able to offer their patients a more balanced view of therapeutic benefits and harms and more realistic explanations of what treatments have to offer, generating more active and trusting relationships; and governments and healthcare authorities should be able to make better decisions about choosing strategies to improve public health.

People trust healthcare professionals to make balanced decisions on healthcare issues at the individual and community levels. We are expected to

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harness reliable evidence, competent expertise, and sensible judgments to inform our decisions, but evidence may be biased or unavailable, and many decisions rely on pious hopes that things will turn out well. Some of the problems and the ways forward are discussed in this theme issue. Have a nice trip.

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Benefits and harms of drug treatments

Observational studies and randomised trials should learn from each other

However international medical science has become, communicating electronically at the speed of light, some fields are still worlds apart. The movement that is subsumed under the banner of evidence based medicine, with its sister movements such as the Cochrane Collaboration or the BMJ's *Clinical Evidence*, aims to evaluate whether the benefits of treatments that had been hoped for actually exist. This relies almost exclusively on randomised controlled trials, in particular in the study of drug interventions. In a world apart is the field of pharmacoepidemiology, devoting itself mainly to detection and systematic studies of the adverse effects of the very same treatments. Adverse drug effects are often unanticipated and are predominantly investigated by observational studies—for example, by using large databases that link routine prescriptions with the occurrence of unexpected disease.

The protagonists of these fields barely know each other: they publish in different journals, write and read different books, and work in different departments. They are even suspicious of each other's methods. Adepts of evidence based medicine doubt whether anything reasonable can follow from observational research; they give the impression that they believe that methods of observational research lag far behind. Pharmacoepidemiologists have hitherto made little use of systematic reviews of randomised trials in their much broader job of assessing causation of harm from a variety of pharmacological, clinical, and observational data.

Yet intellectually, both sides can and should coexist and learn from each other.[1] [w1] Assessment of small effects of treatment will always need randomised trials as its yardstick. At the other end of the research spectrum of all fields of observational research, research into adverse effects of drugs offers the best chances of being as unbiased as if randomised.[2] [3] Each medical question should be approached by using the appropriate research tools[4]—this effectively precludes the idea of a single grading of levels of evidence for all types of research questions.[2]

Individual randomised controlled trials often do not suffice to detect adverse effects, especially if the effects are rare and late.[5] [w2] Systematic reviews of randomised trials have offered little solace so far, even for early and relatively common adverse effects, as adverse events had not been systematically described in similar ways in the individual trials and therefore could not be compared directly for the purpose of a systematic review.[6] In addition, most systematic reviews shun observational research. Although there are exceptions,[w3-w5] even established adverse effects are often not assessed in systematic reviews, presumably because no randomised evidence exists. However, a balance of benefits and harms is the only reasonable way to evaluate interventions.

Randomised trials are good at sorting out what works and what doesn't. Even if they show a benefit, they often do not give sufficient insight into harms. A properly balanced review should include a systematic evaluation of adverse effects by the best methods of observational pharmacoepidemiology. For their part, pharmacoepidemiologists should abandon their exclusive preoccupation with one side of the question and one type of methods: they should explore collaboration with people who conduct systematic reviews or randomised trials. Hidden nuggets might be found by scraping the randomised barrel, as happened in a

Additional references w1-w6 are on bmj.com

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