EDITORIAL

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The Good Old Drugs!

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The Centres for Medicare and Medicaid Services (CMS) blames increasing drug safety concerns for slower growth in health spending.[1] In the Chicago Tribune Inside Health Care column,[2] Bruce Japsen wrote, ''In a twist to the annual government report on health spending, government actuaries listed drug safety problems as a key contributor to the slowing national spending rate on prescription drugs.'' Whilst ''the primary driver of slowing growth of drug spending in 2007 remains the increasing use of generic versions'', the CMS also commented that analysts believe that ''the higher number of safety warnings issued on prescription drugs'', usually lead ''consumers and their doctors to choose older drugs that tend to have better safety records and are generally cheaper because their patents have expired and they are available in generic form.'' The report contends that 'black-box warnings', ''an indication the drug carries safety risks that include potentially life-threatening adverse effects'', are on the increase. According to the report, in 2007 the US FDA issued 68 black-box warnings, while by comparison, there were 58 black-box warnings issued on drugs in 2006 and 21 in 2003.

There are three questions that should be asked relating to the above report.

First question: 'Are we better at finding harm than we used to be?' We think we are, and certainly we seem to find more about risk earlier. Even though the increases in 'black-box warnings' suggest this, is it true that the risks are greater now? Better systems for safety, better awareness and more reporting does not necessarily mean bigger risks.

There is a counterpoised second question: 'Have the risks really changed compared with how they used to be, qualitatively and/or quantitatively?'

A third question might ask whether decision makers are considering that patients are more risk-averse than in the past and are taking actions, including giving warnings, at lower levels of risk? Or are the regulators themselves more concerned about risk than in the past?

There is undoubtedly an increase in reporting of individual case safety reports (ICSR), with an exponential growth in the numbers of reports in the WHO database.[3] We do not have any hard data on any possible change in the nature of ICSR over the years, but I do see more reports of events that are likely to be due to confounding or chance, and I am often told this is because of unfiltered passing on of information, pushed by legal and bureaucratic concerns; we generally also see more event terms noted per report.

The ongoing debate about whether the selective serotonin reuptake inhibitors and isotretinoin may increase the risk of suicide is a possible example of increased reporting that may be confounded. The high levels of reporting have drawn media attention and have had effects on public perception. Here, my argument is not to consider only the aetiological fraction of suicides that may or may not be due to the drugs, but to point to the higher rates of reporting which follow public awareness in a cycle that can promote a negative view by public and professionals alike, and which probably has its effects on regulatory perceptions. It is undoubtedly true that amitriptiline, as the widely used older drug for depression, has led to the death of many people via its cardiotoxic effects, but this is not part of the public debate on antidepressants. There are

many other examples where widespread media reporting for a newer drug can be compared to the much more limited reporting for older products. Rosiglitazone has been widely reported concerning its cardiotoxicity, but the ongoing, very old debate about cardiotoxicity associated with the use of the sulphonylureas gets little mention in the media, let alone the part played by the underlying increased risk of cardiac problems associated with diabetes mellitus itself.

The second question concerns risk perception. As a possible example of changes in quantitative risk concern, QT prolongation causes death in about 1 : 35 000 individuals[4] and not all of these deaths are drug related. QT prolongation has, however, been regarded as a 'major hazard' by the FDA.[5] It so happens that the fatality rate is of the same order as for anaphylaxis after exposure to penicillin, about 1 : 50 000,[6] and we still use penicillins on a routine clinical basis, whereas a drug that prolongs the QT interval will not easily get onto the market now. We should be much more open about setting into context the quantitative aspects of the (low) risks from drugs, and we need to debate those risks in a more consistent fashion, considering the context of disease risk and the risks of older treatments.

Considering the qualitative aspects, are we more concerned about certain kinds of risk? The rofecoxib controversy is a good example of a drug with better safety proposed in one area (gastrointestinal [GI] bleeding) but with a new risk of increased cardiovascular disease;[7] but we did not know that some of the old NSAIDS had the same cardiovascular problem, although we thought they were more GI damaging. Here we should be concerned with overall comparative effectiveness in our risk assessment, as well as considering perceptions about whether the prospect of death from GI bleeding overall is more of a concern than death from heart attack. One suspects that for many, heart attack or stroke would be seen as a worse risk than GI bleeding, even if the mortality rate was the same, but we should try to find out more on relative risk perception.

The third question relates to the broader aspect of risk perception and the ability of regulators to stand as decision makers, 'second guessing' on behalf of society. The re-introduction of alosetron for irritable bowel syndrome (IBS) is an example of where the caution of regulators seems to have been misplaced. It appears that the rare serious risk of ischaemic colitis is worth it for many patients with IBS, even though regulators first thought it should not be marketed.[8] Whatever the real 'risk-to-benefit' balance and whatever pressures were or were not brought by industry,[9] the changed decision indicates the need to consider patient opinions: '… from being traditional and paternalistic to holding a more republican view of public health. The agency would now rather provide the best information for patients and doctors to make their own decisions than to make the decisions in their name …'.[9]

We have old medicines such as aspirin and warfarin that we still use in spite of their many serious imperfections because they are effective. We also learn how to use the old drugs in the best ways to minimize their adverse effects, and we become used to them anyway. We are comfortable with them, like the proverbial 'old slippers'! As the Chicago Tribune article says, using generics is cheaper, but at the same time we may be missing some of the benefits of newer products, by scaring prescribers and patients.

New drugs come along offering better potential benefits, sometimes in areas where there are no real alternatives. These new drugs will have adverse effects and we judge them as they come to light, but those judgements are based on an entirely new and different conceptual knowledge and value base than in older regulatory safety practice. We often need to consider how new drugs compare in terms of benefit and risk profile compared with the older drugs they replace, but we do not have a convincing way to consider comparative effectiveness and risk between old and new drugs because only a small amount of the knowledge is contemporaneous or qualitatively similar.

We do not yet have real answers to the above questions and we do not audit regulatory decisions, certainly not for consistency and trend. We would find it difficult to find measures for some

of the variables concerned, but one can be reasonably sure that drugs such as aspirin, warfarin and digoxin would not be made available if they were judged by today's safety standards.

One point is quite clear: media interest in and coverage of drug safety findings, and the quite reasonable public pressure for transparency in drug safety issues, both play a large and increasingly important role in providing feedback to regulators and industry to ensure that they fulfill their responsibilities. As we have said repeatedly, providing balanced risk information which is really useful to the public and health professionals, is a major communication challenge.[10-14]

The most recent development of an 'Erice Manifesto',[14] was the third in a series of debates organised through Professor Giampaolo Velo, and raised many of the concerns over getting better audit of regulatory practices, along with transparent and contextualized communication. Communication, with education, is highly relevant to the way the public views medicines. Hiding safety matters is not the way to go, transparent and balanced dialogue is, although it is not easy to achieve.

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