COMMENTARY

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Intelligent Risk Communication
Can it be Improved?

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Abstract

Every year, regulators and scientists from academia and industry invest considerable time and effort into drug development, the assessment of safety, and subsequent risk-benefit communication. The observation of everyday medical practice, lay press releases and drug information indicates that all these efforts do not do justice to the work and effort invested. Risk communication is a complex scientific activity, which, when done properly, benefits patients, and when done poorly, may lead to harm. There is much misunderstanding and confusion even between professionals in communicating risk-benefit information, as the association of risk with drug treatment is a difficult concept to accept. It is apparent that the concept of intelligent risk-benefit communication has to be developed extensively on many levels and with the co-operation of everyone involved (patients, physicians, regulators, scientists, journalists, lawyers and the government). This article addresses some key aspects of dealing with the risks associated with drug treatment in everyday practice, as consideration of these risks may be of benefit to all concerned in the future.

Much time and effort has been devoted to risk communication over the years. However, everyday practice indicates that the understanding of risks associated with drug treatment is inadequate and adds to patients' confusion and, not infrequently, harm. This article attempts to address a few aspects of everyday practice in dealing with risks.

The emphasis on *risk* in risk communication is an inappropriate focus. This focus has been reinforced in the last several years by numerous international and national documents.[1-3] Most of these documents refer to 'risk management' and all concentrate on risk. Such an approach seems to be only partly correct, as at the time of licensing of a medicinal product, the efficacy of the product is well understood but knowledge of the risks associated with the treatment is limited.

There is a need to accept that this knowledge will always be limited; that is, all risks will never be identified, despite the development and use of methodologies that could improve the investigation and assessment of risk. Some of these methodologies (e.g. meta-analysis) are used to analyse studies not powered to detect risks. Others using well developed methods (epidemiological studies) or those that include large samples (large simplified safety studies)[4] can never fully reflect the response of the real-life, large population to a new chemical entity.

An example that facilitates understanding of the difficulties of safety assessment in the general population is the length of time it took modern society to start labelling food for the content of peanuts, consumption of which is much more widespread in the population than the use of any man-made pharmaceutical. There are many examples of similar situations, but the easiest way to illustrate this effect is to imagine a city of 1 million inhabitants (large population) or even a smaller one (e.g. the Framingham study, conducted in a small town of about 50 000 inhabitants).[5] In these populations, any event (especially a serious one) can be detected or reported with or without any association necessarily being made

with the drug, as in a large population the event would be expected to occur on nearly an everyday basis. The number of events that occur and the number reported depend only on the size of the observed population. The only exceptions from this rule are the syndromes associated with the use of a specific drug that have emerged and found their way into medical handbooks such as oculomucocutaneous syndrome associated with the use of practolol.[6]

Two additional facts need to be added to this picture. One is that there are no drugs (including placebos) that have no adverse events associated with their use. Second is the expectation of patients and members of the public that drugs will treat or cure them without causing them any harm. These above-mentioned aspects illustrate the difficult situation being faced by everyone in the pharmaceutical field. The problem applies not only to the pharmaceutical industry, but also to regulators, scientists, physicians and other healthcare professionals, communicators on safety, patients and, in the majority of cases to the detriment of all the above, lawyers and the media.

Extensive work and brainstorming devoted to improving risk communication has been undertaken in recent decades. The *Erice Declaration* of 1997[7,8] and the subsequent Erice conference in 2006[9] delivered many important thoughts and solutions for safety communication.

Most of the definitions of 'communication' cover the fact that it is a two-way process and, therefore, the communicator (no matter how ethical, scientific, precise and effective), in addition to following all the set standards, has to make sure that the message has been appropriately understood. This is a very difficult task as, according to the official report of the UK Treasury, about 30% of the UK citizens are functionally illiterate and innumerate,[10,11] a percentage that matches that found in the US population,[12] where 90 million people (about 30% of the population of 300 million) share the same features. It appears, without searching through other sources, that in many parts of the world such statistics may look similar or even worse. So even the most carefully prepared communication escapes a significant percentage of the audience, who will not be able to understand the content.

Science is becoming increasingly complicated, and therefore frequently adds to the level of confusion in the minds of healthcare professionals and members of the public. A substantial number of healthcare professionals have difficulty understanding the information covered by professional journals. It consequently becomes more difficult to explain to the patient what certain statements mean for them. Take for example, the statement, "the risk of experiencing bleeding or stroke in patients stratified by age and sex, and adjusted for confounders, is 3%". Translating this risk information to the patient even if the physician understands it perfectly may prove to be challenging. In addition, the healthcare professional may be faced with a response from the patient that is, "What do you mean doctor, 3%? Either I will have it or I will not?" From the patient's perspective, it is either 0% or 100%.

The example given above is much simpler than many of the situations physicians frequently have to deal with. A more complex example would be:

"The mean coronary-artery calcium score after trial completion was lower among women receiving estrogen (83.1) than among those receiving placebo (123.1) (P = 0.02 by rank test). After adjustment for coronary risk factors, the multivariate odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared with placebo were 0.78 (95% confidence interval, 0.58 to 1.04), 0.74 (0.55 to 0.99), and 0.69 (0.48 to 0.98), respectively. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For coronary-artery calcium scores of more than 300 (vs. <10), the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence."[13]

Clearly translating this message for the patient is rather challenging. It appears therefore that advanced clinical research helps risk communicators only to some extent, despite complying with transparency and scientific standards.

Most of the very well thought-out communications are lacking in an important aspect, that is, the real perspective of the presented risk (and benefit). For example, the conclusion of a study after 7 years

states *"…was associated with an increased risk of fatal stroke (59 vs. 39 events; hazard ratio, 1.49; 95 percent confidence interval, 1.00 to 2.24; absolute risk increase, 0.7 per 1000 woman-years"*.[14] Such a statement would be a topic for extensive discussions on scientific and regulatory forums. In most situations like this, there is no explanation of what such a statement means. As the statistical significance was achieved in the seventh year of treatment, the data indicate that there need to be 10 000 patients continuously treated for at least 7 years to see a significant increase, which materializes in seven additional cases of fatal stroke in the treated population. There are several other unaddressed issues here: to what extent were the treated and control groups representative after 7 years of the study (there is always a substantial attrition with time)? Were the subgroups sufficiently large to make a comparison and draw conclusions? Would the risk factor increase with age (potentially incidental despite difference with control)? And would the treatment be used in real life for 7 or more years to even observe such a situation in an uncontrolled setting? So, if in normal conditions the drug is taken for 6 months, is the finding relevant at all, especially if the placebo group could have diminished more markedly over time having no benefit at all from the treatment? The other question relating to human (and animal) studies would be; does statistical significance (in the example above $p = 0.049$) apply, and would it translate from statistical to real biological difference, risk or benefit? There are very many other examples similar to this in the literature, which explains the fact that numerous communication problems, predominantly arising from the communication of risk, have been encountered over the years.

There is yet another aspect that needs to be raised: science is constantly changing and applications of different methods to the same set of data can provide different outcomes. This effect could have been observed in the use of the same data for analysis of phentermine-fenfluramine toxicity[15-18] and, more recently, in the analysis of the Women's Health Initiative (WHI) data. The first analysis of data from the WHI study presented in the published paper clearly made a huge impact by undermining the benefit of hormone replacement therapy (HRT) in postmenopausal women.[19] The subsequent analyses, which looked at subgroups with consideration given to other factors of the studied population, largely changed the conclusions of the first paper.[13,20,21] A less contentious example is the diversity of advice regarding the use of aspirin to reduce the risk of colon polyps.[22] From a strictly drug-safety-assessment perspective, two tools (Q-scan and Lincoln Technologies) were used for data mining with exactly the same input, resulting in significantly different disproportionality results.[23] In such an environment, delivering the information on risk/benefit is very complex.

However, as science is in a state of continuous development, we need to follow the scientific concept stated by Sir Austin Bradford Hill, "All scientific work is incomplete – whether it is observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer on us the freedom to ignore knowledge we already have, or to postpone the action that it appears to demand at a given time",[24] and deliver the communication accordingly.

There is no perfect remedy to this problem, despite all the work that has been done by scientific and regulatory minds on the subject of risk communication. There is no question, however, that it can be done better.

Intelligent risk communication should be delivered as 'risk-benefit communication', and there should be a mechanism to make sure that the information provided is understood by all, including the patient. The easiest part of the communication is the detected 'risk' (usually one, as the overall risks are rarely considered in a single communication). The benefits are known, so there is a need to find and communicate the relationship between the risk, its incidence in the population, impact on patients' and public health and the established benefits. The difficulty of assessing risk versus benefit still exists as, despite many efforts over the years,[25-28] there is no quantitative method for assessment of risk-benefit that would be comparable and facilitate delivery of a clear and easily understandable message.

To achieve the goal of scientifically sound, well prepared and, hopefully, well understood and not misinterpreted risk-benefit communication, we need to be inclusive, that is, all parties (patients, public,

healthcare professionals, regulators, scientists, media lawyers and 'trusted organizations', e.g. scientific societies, patient groups) should be involved. In contentious cases, one needs to make sure that the right audience is targeted at the right time, that the information is delivered in the appropriate perspective, and in a context and language that the majority of people can understand.

Looking towards the future, the most important action is the setting up of an educational programme on drug treatment. The wider public need to understand what risk-benefit means, and understand that drugs are associated with risks just as much as any other activity that we undertake in life (car driving, skiing, skydiving, flying etc.). As much as toxicity is unexpected from the drug that should treat us, it may not be, in individual cases, different from the food that should feed us, but it very rarely may cause severe allergic reactions or even have fatal consequences.[29-32] Despite our strong belief that drugs should only treat and not cause any harm and that all physicians follow Hippocrates principle '*primum non nocere*' (first do no harm), it is unfortunate that, in large populations exposed to a drug, anything can rightly or wrongly be associated with the use of that drug. For the benefit of a patient, the general population and public health, the emphasis should be on safety issues that affect substantially large groups of patients and not on issues that are so frequently marginal despite extensive media coverage.

When analysing the most frequent hospital and outpatient adverse drug reaction (ADR) reporting, it is not surprising to find that the vast majority of ADR reports come from well known drugs that have been used for many years: NSAIDs, warfarin/anticoagulants, antiplatelets and diuretics.[33,34] Somewhat illogically, these reports are not attended to sufficiently, as scientific and regulatory resources are predominantly drawn to ADRs of lesser incidence, because of the interests of the media and lawyers. Most, if not all, widely publicized issues over the last 10–15 years have an estimated incidence of <1 : 1000 exposed patients or even below.[13,14,18,19] They all deserve attention, action and adequate communication. From the perspective of public health as a whole and of the individual patient however, the message that drugs are safe and effective and that regulators and the vast majority of independent and industry scientists are scientifically sound, as well as being true, delivers a much improved message to the population. This message for some reason has not recently been delivered adequately or has even been lost altogether.

Our efforts in years to come should focus on education about risk-benefit, conveying the message to the public that there is no benefit without a certain degree of risk and (after very stringent scrutiny) that the drugs provided to the public are largely safe. The absence of effective communication can result in harm to patients who, by stopping their medication (frequently without even talking to their physicians) expose themselves to numerous unnecessary risks. For example, pregnancies and venous thromboembolisms without contraceptives,[35] depression and suicides without antidepressants,[36,37] and uncontrolled diabetes due to the content of product information.[38] There is a clear message that seems to be frequently forgotten, that the risk of adverse effects resulting from failure to take a prescribed drug are real and not in fact very rare, unlike the most publicized drug-related adverse effects, which are rare to very rare (<1 in 1000 or 1 in 10 000 patients).[13,14,18,19]

Most of the above-mentioned harmful effects to the individual, and to public health as a whole, are the result of irresponsible activity within the media (presenting 'wonder' or 'killer' drugs) and the overactivity of the legal profession driven by lucrative fees. These behaviours cannot be fought off by even the most effective risk-benefit communication as they are clearly profit driven. We should hope, however, that with a degree of education directed at the general population, patients, medical/pharmacy/nursing students, postgraduates (at different levels of their careers), and scientists, some changes will be achieved.

There is no perfect formula for ideal risk-benefit communication, otherwise there would not be so many presentations, publications and regulatory documents devoted to this topic. However, here is a list of thoughts that apply specifically to communication about the risk-benefit of marketed drugs. We should keep them in mind while planning, delivering or observing future communication activities.

- The first point of our approach to risk communication should be to concentrate on safety, i.e.

risk-benefit (or benefit-risk) communication and *not* 'risk communication'. The thinking process and activities should be refocused to 'risk-benefit management'. To reflect this, all of the formal regulatory and International Conference on Harmonisation (ICH) guidelines should be renamed to 'Risk-Benefit Management' and 'Risk-Benefit Communication' or a similar name to reflect the fact that there is no benefit of drug use without a risk and vice versa.

- To work with all parties constantly on risk-benefit assessment so when an unexpected communication is necessary because of a newly identified 'risk', the risk-benefit statement can be delivered in an understandable way according to best principles. It is necessary to be proactive, frequent and clear in all communication, and include trusted organisations (e.g. scientific societies and patient groups) during everyday work, which will facilitate their input into improved communication.
- To consider and gradually establish a relevant education strategy as early as possible, starting with healthcare professionals, patients, media, regulators, etc., but also considering school-level education (sex education was introduced to schools on risk-reduction basis; a similar approach should be taken to incorporate concepts of drug risk-benefit into health education).
- Always provide perspective to the risk-benefit information so that potential misinterpretation and poor decision making on the part of the patient and prescriber is diminished and understanding facilitated.
- Deliver the best quality science (scientific communication) with messages that would not be confusing to professionals.
- Allow and justify patients' informed consent to treatment as it is allowed with other risk-associated activities, i.e. travelling, smoking, alcohol consumption, dangerous sports.

The implementation of intelligent and effective risk-benefit communication is a long process. Delivering any of the above-mentioned points would improve the current status. Delivering all, however, is a very challenging task. Over the past 3 years, substantial progress has been achieved in regulatory risk communication (sometimes even risk-benefit communication)[39,40] in many ways, for example, form, source and content, which indicates that we are moving in the right direction. The agencies utilize websites, blogs, leaflets and all previously used methods of risk communication. Language is being checked for readability and there is greater involvement of end users in creation and delivery of the messages. The scientific media need to move swiftly also, as this will influence the overall understanding of scientific data and reporting of medical issues by the general media. Much work needs to be done, but for further progress and future success we need to work together to win the concept of 'intelligent risk-benefit communication'.

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