EDITORIAL

Drug Safety 2009; 32 (6): 449-452
0114-5916/09/0006-0449/$49.95/0

Understanding and Communicating Key Concepts in Risk Management

What do we Mean by Benefit and Risk?

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Words can be used to express ideas and knowledge in ways that are not intended nor understood in the same way by the recipient. Following previous papers on definitions by Lindquist[1] and Hauben and Aronson,[2] in this editorial we explore some key concepts in risk management. We try to link the concepts with current trends, and try to find words that will support such concepts without moving far from their generally understood meanings.

1. The Positive Aspects of Therapy

Modern therapy is based on pharmacological knowledge of how a medicine can work in alleviating symptoms, altering physiological or pathological processes (including products used as diagnostic tools). This is utility.

Pre-marketing evaluation is concerned with how the medicine works in patients; how frequently and to what extent. This is done in selected patients (and healthy volunteers) to allow for the clearest uncomplicated analysis of efficacy. This efficacy is usually compared with a control group of patients, which further defines efficacy compared with a placebo or another treatment. At this point it is *efficacy* and not *benefit* that has been defined.

We must be concerned about the effectiveness of medicines in day-to-day clinical practice, as opposed to the concept of efficacy[3] measured in the clinical trial situation. Although the two words are often used interchangeably in everyday language, there is an increasing literature that makes the distinction between the two. It is also implied, or stated in some studies, that effectiveness is a better measure of the benefit of treatment. This is true, but benefit depends upon effectiveness (and efficacy) but at the same time is not the same as either.

Benefit is 'something that aids or promotes well-being'. Well-being is a subjective, value judgement. One can guess at benefit to an individual or society, one can even devise some efficacy measures that many would agree indicate that benefit has been gained, but these do not measure true benefit, particularly in an individual. A patient may well benefit from a placebo, or may judge the best effects of a medicine to be inadequate. For example, lowering blood pressure in a hypertensive patient may work well, but the patient may only be aware of troublesome adverse effects, or nothing at all. In this situation s/he may feel there to be no benefit. Benefit can only be judged if it includes patient expectation and completely measures the fulfillment of that expectation.

2. The Negative Aspects of Therapy

On the negative side of therapeutics we know that all treatments present a hazard: there is a potential for harm. This is usually defined by toxicological testing, analogous to the procedures used to define utility.

Pre-marketing human studies are usually aimed at testing efficacy more than safety.

In clinical trials, we obtain limited information on the risk of harm: the probability that damage will occur. The process is analogous to that defining efficacy. Unfortunately, this process of defining risk is much less complete than that defining efficacy, since the risk outcomes are much less frequent than the targeted efficacy.

Once a medicine is used in regular clinical practice, and sufficient numbers of patients have been treated, one has a much better idea of risk. One can also see the degree as well as the frequency of harm done to patients. Harm is the true converse of benefit: the full extent of harm to an individual is very much a subjective issue; for example, an older person may accept impotence with some equanimity, but a young person will probably be much more concerned.

3. Overall Patient Assessments

In assessing overall patient outcomes, we may use 'quality of life' instruments (QOLIs); usually questionnaires, or predetermined questions used at an interview, which contain assessment items thought by investigators to be significant for the particular investigation. QOLIs are useful in determining the summary balance between beneficial and harmful results of treatment (a 'satisfaction' score) in a patient or group of patients, but they have limitations.

One issue is the large numbers of QOLIs available for use. A recent example is 116 tools for assessing the persistence of non-cancer pain,[4] 43 of which the reviewers found 'convincing'. The authors conclude, however, that, 'no one assessment instrument captured all the constructs of persistent pain'.

Another important factor is that the questions answered in QOLIs are predetermined. This may introduce biases in the results. Questionnaires, in their phrasing, often portray attitudes and, in the combinations of questions themselves, may have inherent biases. Most of these issues are well recognized, but the accepted between-group comparison reliability is only between 0.5 and 0.7. The within-patient reliability should be to the order of 0.9 but one still wonders about sensitivity.[5]

Nowadays we often present results in quality-adjusted life-years (QALYs), which allows for varying times spent in different health states, which is essentially a health state area under the curve. The basic limitations of QOLIs may still apply, but QALYs are closer to patient-derived assessments since they also measure variation with time, involving multiple health variables and differing time variables. Sometimes, for pharmacoeconomic analysis, a third variable, that of cost, is considered. On the other hand, in trying to determine which is the 'best' therapy, the comparisons of interventions across different dimensions is fraught with logical hazards where gains in one dimension need to be offset by losses in another. Considerable value judgement is needed.

Although QALYs may be valuable from a broad public health perspective, the richness and paradoxes of human perception may be buried in the data and obscured when only the summary information is used in making decisions. While chronic pain may be a very special area in quality-of-life assessment, Grimmer-Somers et al.[4] gave a very good account of the various factors that might be included for a complete assessment of a patient: the result is strikingly complex.

4. Some Dimensions of Perception

The subjective responses of patients, to benefit and harm information, depend upon their perception (becoming aware of something via the senses). We perceive pain, fatigue, well being, etc.

We talk of 'risk perception', which has a completely different connotation: perception of risk (and indeed of effectiveness or efficacy) is an imaginative, intellectual, evaluative dimension in which we consider how much we understand and accept about the probability that different kinds of harm may occur.

There is an interaction between actual experience of benefit and harm that will influence the way in which a person evaluates information provided to them on risk and benefit. All of us are considerably influenced by previous experience: subjective experiences, such as our previous actual perception of pain, will considerably affect

an evaluation of the risk of pain in any possible future situation.

5. Some Consequences for Risk Management

Does any of this matter? It is very important to understand and communicate to patients that efficacy, and even effectiveness and risk, only indicate probabilities for a good or bad result for them based on normative information. All the necessary information must be easily available to doctors to allow them to communicate this as completely as possible. We are far from being able to do this fully, but progress in information technology and informatics will help us achieve this goal where such infrastructures are available.

As increased numbers of human subjects are involved in the outcome of research studies, not only is there more relevant quantitative information available, but more subjective information *should* be available and taken into account. After all, any therapy has the primary aim of satisfying the individual patient: not society, not the government, not academics and not the pharmaceutical industry. As it becomes available, such qualitative and quantitative effectiveness and risk information should be interpreted alongside each other and should modify the utility/hazard information and the efficacy/risk information.

Differences in human subjective perceptions may lead to wide differences in the value interpretation of any results. Is a medicine that has a 70% response rate in reducing the duration of a disease process by 30% regarded as efficacious or not? Is a risk of a fatal adverse reaction occurring in 1 in 30 000 acceptable to society as a whole or to an individual patient about to take the medicine?

Health professionals not only need complete and useful information, but it is essential that their conceptual framework is clear concerning different types of information. They need this in order to assess the merits of a medicine in different patient contexts: the expression 'benefit-risk' is still in widespread use to indicate the *potential* positive and negative attribute balance for a medicine or other treatment, and there is great danger that patients will interpret this wrongly. As outlined above, this equipoise is illogical, since benefit is a concrete but subjective gain, whilst risk is the assessed potential for harm: we should talk of effectiveness-risk, unless we have QALYs when we can talk about a composite, overall benefit-to-harm balance.

It should be routine to find out about the individual patient's needs and expectations of therapy. Patients should, through their medical advisors, be given as much information as they can handle on the effectiveness-risk balance, and some explanation of how it may apply to them. So-called 'evidence-based medicine' is heavily biased towards the use of epidemiological, effectiveness information. This makes good sense from the public health perspective and for cost containment. On the other hand, there has to be a large interpretive aspect in applying effectiveness and risk information to an individual patient as well as follow up to ascertain what benefits, and possibly harm, may have been the result. Those who advocate evidence-based medicine seem to over-promote the idea of fitting a patient to a norm, rather than adapting general information for individual use. Thereafter, patients should be carefully followed up to determine the actual benefit and harm they experience. It is noteworthy that in other medical paradigms (such as traditional Chinese medicine [TCM] and homeopathy) very close follow up of the patient's signs and symptoms is more important than the disease process itself. This may be important for their continued popularity in patients' eyes, since each treatment is individualized and changed according to their progress, and therefore may be seen as more responsive to the patient's needs.[6,7] Harm from treatment needs to be considered in more detail than we do at the moment. It is not sufficient to record the objective information on an adverse reaction. If an adverse reaction to a medicine occurs, we should ask, and record, what the patient feels about it. Information on the patient's relevant background experience will again aid interpretation. Is this the first adverse drug reaction for example? How bad was the last experience? Compared with this one?

Our current gaze on the use of information from epidemiology and controlled studies must

be balanced by a proper consideration of *all* patients' needs. Maximizing *individual* benefit and avoiding harm is the only acceptable ethic in clinical medicine.

Acknowledgements

No sources of funding were used in the preparation of this editorial. The authors have no conflicts of interest that are directly relevant to the content of this editorial.

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