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Pharmaceutical Risk and the Quality of Life

Beat Hiltbrunner and Andreas Breitsprecher*

Introduction

“I am giving you medicine, not a poison.” What appears to be an oath from the pen of a doctor or pharmaceutical representative is in fact from the drama “Nathan der Weise” by the German poet Lessing and was written in 1779. However, this quotation is still relevant today. Apart from their benefits, drugs always entail a risk. Thus, closely associated with the quotation from Lessing are questions with regard to drug safety and the ratio of accompanying risks and a possible increase in the chances of cure or improvement in the quality of life.

Individual acceptance of risks generally, or those posed by pharmaceuticals specifically, is a function of more than their frequency and severity. It is also a function of what benefit one expects to gain from assuming a risk, and both the evaluation of risk and the evaluation of benefit tend to be quite subjective.

Recently, investigators have attempted to get a better grasp of risk and benefit perceptions through “quality-of-life” studies which ask patients to complete questionnaires.¹ The main objective of this paper is to briefly review what it is that these instruments attempt to measure

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¹ See generally, e.g., QUALITY OF LIFE ASSESSMENTS IN CLINICAL TRIALS (B. Spilker ed. 1990). See also, Merz, *An Empirical Analysis of the Medical Informed Consent Doctrine: Search for a Standard of Disclosure*, *infra* 27, at 54.

and the potential for use of such research in the evaluation of drugs.

Risk Acceptance Generally

During our life, we are confronted with an indeterminable number of risks. We have to estimate them and then decide whether we are prepared to take these risks in the light of the expected benefits. It is well known that there is no such thing as zero risk. Nevertheless, there's a growing tendency in society to avoid taking risks. A sort of "zero-risk society" is emerging — a society that is attempting to protect itself as far as possible from everything forever. This is in fact a paradox. It is precisely in the western industrialized countries with growing technical advance and affluence that we are living in an environment where risks are increasing at a similar rate. One would be justified in claiming that industry tends to increase the number of risks, not only for some individuals but for society as a whole. One can think of the dangers involved in industrial production and use and in the problems of subsequent disposal of wastes. No one would wish to dispute the fact that the use of the car — a symbol of technical progress — involves enormous risks. The same applies to the possible consequences of everyday stress, incorrect nutrition or the consumption of nicotine and alcohol and environmental pollution. Viewed objectively, the risk-shy industrial citizen is thus exposing himself to very serious risks.

We have to accept some risks. However, we are confronted with the problem of trying to fit risk acceptance into a scientific framework. What is acceptable in the individual case, and what is not? And by which criteria and with which means can the individual determine this?

In this context, what certainly plays a role is the fact that people associate certain things with the subjective idea of high or low potential risks — regardless of the actual existing dangers. Thus, in statistical

terms, the probability of dying in a car accident is significantly higher than death from the effects of a drug.² Nevertheless, drugs as a whole are classed as being more dangerous. The benefit/risk evaluation applied to drugs gives a completely different result compared with the evaluation in the case of a car.

Apart from a lack of information, the reason is certain also to be found in the tendency toward different evaluation of perceptions, which often confuses the desirable with the actual. The daily report on automobile accidents is certainly not as spectacular as an air crash or a dramatic drug offense report. Nevertheless, in the decision-making process, everyone daily makes his own, generally subjective, risk evaluation on the basis of information available to him. This also applies to the sensitive area of drugs.

Drug Risks

The pharmaceutical industry contributes to the existence of risk in two ways. First, research and technical and administrative activities give rise to possible risks which affect safety of the workplace, the inhabitants of the surroundings or of the whole environment. These are factors which are becoming more and more important in society. This branch of industry invests considerable sums of money and human resources in the investigation of industrial risks and in the development of suitable technologies to reduce risks posed by its activities. Second, the products of the pharmaceutical industry are possible sources of risk. As noted earlier, drug safety has long been a matter of concern. Medicaments must meet in particular the three main criteria of "quality", "efficacy" and "safety" — safety clearly being the most sensitive area.

The ethical responsibility of science, medicine and the pharmaceutical industry to minimize drug safety is undisputed. A true

² Heilmann, *Das Arzneimittel als Risiko*, PHARMA DIALOG 82 (1984).

awareness of the existence of drug-related risks among the broad population first emerged in the 1960's as a result of the thalidomide tragedy. This case initiated a radical change in the public's perception of risks associated with the effects of drugs.

In the past, evaluation of the risk of drugs was based on spontaneous reports of side effects, post-marketing surveillance studies or literature evaluations. Nowadays, much more precise studies of drug risks are required. They include extensive compilation of side effects in the international context, safety evaluations in clinical studies, and biochemical and genetic studies. Pharmacoepidemiology, a relatively recent branch of science, tries to achieve progress along the path to greater drug safety by international networking and worldwide data exchange.

Yet, it would be utopian to believe in the possibility of developing, in the foreseeable future, medicaments without more or less severe adverse effects. One has to live with the risk associated with drugs, but the risk has to be viewed as a function of the therapy. Serious risks tend to be rare and minimal risks comparatively frequent. The central aspect in the determination and evaluation of drug risks is to achieve the maximum possible benefit in conjunction with the minimum possible risk of adverse effects to the patient.

Which risk of adverse effects is acceptable or unacceptable in the individual case? What standards must be set? In the case of life-threatening diseases, such as AIDS or cancer, answers are fairly easy to obtain. However, in the large number of chronically stationary diseases, the degree of a successful treatment tends to vary over ranges which are difficult to measure.

Risk and Quality of Life

There is no doubt that the introduction of effective antibiotics against tuberculosis since the middle of our century has resulted in an improvement in the quality of life of tuberculosis patients. However, an attempt rigorously to measure quality of life has only recently taken place.³ The importance of such evaluations in connection with drug treatment is increasing insofar as people are living longer, and the quality of life is of increasing priority to older people.⁴

Improved quality of life has traditionally been regarded as an inevitable consequence of declining disease or life-prolonging measures. However, it has been shown that the quality of life, as patients assesses it, may deteriorate despite an “objectively” successful treatment.

If the risk of dangerous side effects is high compared with the benefits, the drug usually has to be withdrawn from the market. If the risk is comparatively small and the benefits are large, a risk/benefit assessment is also straight-forward. However, the risk/benefit ratio of most marketable medications fall between these two extremes. In such circumstances, the results of quality-of-life studies can aid doctors and patients in choosing to pursue a method of treatment.

Also, quality-of-life information may be unnecessary if, using conventional disease parameters, the therapeutic efficacy of a new drug is clearly superior to existing treatments. Yet, such information may be very valuable where conventional clinical parameters cannot distinguish alternative therapies. Quality-of-life measurements of apparently equally effective methods of treatment may, if the profiles of the side effects or the action mechanism of a new medicament differ, help patients to decide between possible treatments.

³ Luce, *QoL and the Pharmaceutical Industry: A Perspective*, QUALITY OF LIFE AND CARDIOVASCULAR CARE 191–192 (1988).

⁴ Wertheimer and Nickman, *Drug Therapy and Quality of Life*, QUALITY OF LIFE AND CARDIOVASCULAR CARE 13–22 (1985).

Possibilities and Limits in Practical Use

The term “quality of life” usually covers five dimensions which constitute the main areas of human well-being: physical, social, intellectual, emotional and economic. There are two general types of quality-of-life studies. Some investigate general health studies, and others examine specific diseases. Both employ questionnaires which have to be completed by the patient, but such studies pose a number of questions. Particularly difficult is a suitable method of measurement for comparative evaluations of the quality of life.

The use of general health questionnaires is particularly suitable to compare the quality of life of patients with different diseases or treatment. However, they do not tend to be sufficiently sensitive to differentiate between the effects of similar treatments.

Disease-specific quality-of-life investigations are used to study particular aspects of a disease, for example, the effects of different treatments on the quality of life, their different benefits and their different risks. They cannot be used for other diseases. If the influence of two different hormone treatments on the quality of life of women in the menopause are studied, questions regarding the use of a wheelchair, the need for assistance to move from the bed or the inability of the person to dress herself may be of no importance. In contrast, hot flushes and dryness of the vagina have major impact on the quality of life of these patients but not of patients with chronic polyarthritis or hereditary diabetes melitus.

Quality-of-life instruments which are developed for a particular patient population are often not transferable to patients across cultures. Adapting instruments to new cultural or linguistic conditions is usually a time-consuming and expensive process.

Additional matters further complicate quality-of-life studies. They can be influenced by a wide range of health and demographic

characteristics. In order to separate treatment effects on patient quality of life from other considerations — for example, concurrent diseases — it may be necessary to select subpopulations of patients. This may lead to loss of general validity of the results, a matter with potentially important regulatory consequences.

Studies to determine treatment related improvement in the quality of life may be particularly important in the case of chronic diseases such as rheumatoid arthritis, in advanced stages of cancer, or asymptomatic diseases such as essential hypertension. In the case of progressive diseases, such as cancer, an improvement of the patient's quality of life as a result of therapy may be interesting but not satisfactory unless the duration of the improvement is measured. Unfortunately, few validated quality-of-life instruments can be used repeatedly every two to four weeks.

Studies on the effects of treatments on the quality of life of children, elderly people and the mentally retarded entail special difficulties, and the first steps to resolve them have only just been taken. Additional problems arise from the effects which the treatment of these patients have on their social environment — especially on parents or spouse.

If a treatment leads to an improvement in the parameters of the disease, as well as in the quality of life, the therapeutic intervention is useful. If improvement is shown to the advantage of one drug over another, depending on economic circumstances, health authorities may be more willing to permit or even to favor its use.

Conclusion

Quality-of-life research is generally classified under the “soft sciences” and may not offer the precision that some people would desire. Yet, studies in certain cases, make it possible to record quantitatively the personal risk assessment of a patient and to take the

results into account for a risk/benefit analysis. Such studies can be used to complete a registration dossier as a parameter of efficacy. Because of their potential, they can also be used to study the influence of a treatment on the social environment. Therefore, they may figure into price negotiations. However, quality-of-life evaluations are in their infancy and still entail uncertainties and problems.

Until recently, quality-of-life research has been primarily done at universities. However, over the past ten years, the pharmaceutical industry has begun to play a role.⁵ In the future and particularly as some of the scientific difficulties are overcome, it is expected that the pharmaceutical industry will become even more active in planning, implementation and evaluation of quality-of-life studies.



⁵ Bombardier, Ware, Russell, et al., *Auranofin Therapy and Quality of Life in Patients with Rheumatoid Arthritis*, 81 AM. J. MED. 565-578 (1986). Croog, Levin, Testa, et al., *The Effects of Antihypertensive Therapy on the Quality of Life*, 314 N. ENG. J. MED. 1657-1664 (1986).