Translated from *Rev Prescrire* May 2014; 34 (367): 381-385

Determining the harm-benefit balance of an intervention: for each patient

Abstract

● The decision on whether or not to offer a patient a medical, diagnostic, therapeutic or other type of intervention is mainly based on the harm-benefit balance of this intervention for that particular patient.

● The benefits that matter most are those that correspond to a tangible improvement for the patient rather than improvement in a surrogate endpoint. The harms include the various potential or common adverse effects and drawbacks.

● The harm-benefit balance of an intervention is first evaluated at the population level. Evaluation of the benefits therefore takes into account the strength of the evidence obtained in clinical trials, the magnitude and probability of the benefits in these trials, and the profile of the patients enrolled. Evaluation of the harms involves identifying the drawbacks and amassing a body of evidence to determine potential adverse effects. Evaluation of the adverse effects also takes into account particular situations (age, pregnancy, concomitant diseases and treatments, etc.) and the probability and consequences of error.

● The harm-benefit balance cannot be reduced to an artificial, fixed mathematical ratio. Its assessment occasionally involves a degree of subjectivity. It is sometimes biased due to manipulation of the data.

● At the individual level, the harm-benefit balance depends on: the characteristics, objectives and values of each patient; the healthcare professionals involved and the medical and social environment. It is best evaluated in collaboration with the persons concerned, so that it can provide a basis for shared decision-making.

● The harm-benefit balance of an intervention can change. Its periodic re-assessment, taking into account new evidence and any changes in the patient's situation, provides an opportunity to re-examine the decisions taken, in the patient's best interests.

Rev Prescrire 2014; 34 (367): 381-385.

All interventions, whether diagnostic, therapeutic or preventive, are performed in the hope of obtaining certain benefits but are associated with certain harms (**a**)(1,2,3). Taking both of these aspects into account, i.e. evaluating the harm-benefit balance, is an important step when making decisions about a patient's care.

Which benefits and which harms are considered? How are they assessed, evaluated and compared? Why refer to harm-benefit "balance" rather than "ratio"? In practice, how can we use the concept of harm-benefit balance to help patients?

Without claiming to be exhaustive, this article aims to provide some points to consider in order to facilitate discussions between healthcare professionals and with their patients. It is based on the experience of *Prescrire*'s editorial staff and group reflection, as well as on textbooks on evidence-based medicine.

Implications of the terms "benefit", "harm" and "risk"

The expression "harm-benefit" balance is more appropriate than "risk-benefit" balance (4,5). This is because, while a "benefit" is assumed to be real and proven, a "risk" is perceived as potential and hypothetical (6). The difference in these implications creates the impression that any intervention will inevitably be beneficial for all patients, albeit to varying degrees, while its drawbacks will only occur occasionally.

The word "risk" conceals the existence of frequent drawbacks (6). For example, effective vitamin K antagonist therapy requires all patients to adhere to a strict treatment schedule, to undergo regular blood tests, to take dietary precautions,

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etc. (7). And certain surgical interventions require hospitalisation, followed by a period of reduced activity. These are not risks, but drawbacks to which all patients are subjected. In this article, we use the word "harm" to mean all of the common or potential drawbacks and adverse effects of an intervention.

Assessing the expected benefit based on clinical evaluation

One of the steps in determining the harm-benefit balance of an intervention for a patient is to evaluate the efficacy of this intervention in a sample population, ideally in well conducted clinical trials.

Take into account benefits that are useful to patients, based on their own objectives. When an intervention is being considered, it is usually in the hope that it will provide some meaningful benefit for the patient (**b**). In clinical trials, the endpoints that evaluate meaningful benefits are clinical endpoints, perceptible by the patients concerned (8). Examples include a reduced risk of premature death or disability, shorter disease duration or a decrease in symptom intensity.

Knowledge of the natural history of the disease plays an important role in determining which clinical endpoints are relevant (8). For example, in the case of the common cold, reductions in the intensity and duration of discomfort are relevant endpoints. For a disease that is frequently fatal, the relevant endpoints are often survival and quality of life.

However, the benefits demonstrated in clinical trials using robust clinical endpoints are not always meaningful to a particular patient. This happens for example if the patient's main objectives are family-related, professional, financial or social, rather than medical (9).

Look beyond surrogate endpoints. A change in a non-clinical endpoint may be portrayed as a benefit: for example, a decrease in blood glucose concentration; an increase in bone density; improvement of a radiological finding (1,2,8,10).

In practice, determining the efficacy of a treatment using a surrogate endpoint does not guarantee that it is useful for patients. Clinical trials have shown that in patients with type 2 diabetes, gliptins reduce blood glucose concentration more than placebo (11). But as of 2014, there is no evidence that these drugs reduce the risk of the serious complications of diabetes, or that they prolong survival. In short, there is no evidence that diabetic patients derive any real benefit from these drugs (11,12).

Sometimes, in the absence of a better alternative, surrogate endpoints should be taken into account, provided that the evidence consistently points to a correlation between the surrogate endpoint and tangible clinical benefit (8). Nevertheless, demonstration of efficacy using a relevant clinical endpoint is always more meaningful than demonstration using surrogate endpoints.

Demand robust evidence. The strength of the evidence for the efficacy of an intervention, derived from its clinical evaluation, is always open to discussion (1,3,13-15). It is more robust when several comparative randomised trials of high methodological quality yield consistent results or when the results of a meta-analysis of all the high-quality trials, both published and unpublished, are unambiguous. Evaluation based on non-comparative trials, or case-control studies, provide lower-level evidence.

Did the trials address the questions that need answering? Even when clinical evaluation has provided high-level evidence, the trials may not have addressed the questions that healthcare professionals and patients want answered.

Interventions are sometimes only compared with the absence of intervention or placebo, rather than with a standard intervention (16). Or the trial participants may have been very different from the patients encountered by healthcare professionals: perhaps they were younger or had different health problems (10). In such cases, the trial results or meta-analyses of these trials tend not to provide the information required to determine the harm-benefit balance of the intervention for a particular patient.

Take into account the magnitude and probability of the benefits. An intervention is rarely completely effective in 100% of cases. For example, it may prolong survival in 1 in every 5 patients treated, or only partially improve symptoms, by reducing but not eradicating pain.

Evaluation of the benefits of an intervention is probabilistic. It is important to take into account the magnitude and the probability of the demonstrated efficacy. For example, two randomised trials that included a total of about 40 500 patients showed that low-dose *aspirin*, initiated during the acute phase of a confirmed ischaemic stroke, reduces the risk of death or serious sequelae (17). This conclusion is based on high-level evidence. The magnitude of the expected benefit is high: prolonged survival and less severe sequelae are important gains. But its probability is low: for every 1000 patients treated, after 1 to 6 months, *aspirin* prevents death or dependence due to sequelae in about 13 patients. In other words, after 6 months, over 98% of treated patients will have derived no benefit in terms of survival or serious sequelae.

In certain situations, even if the hoped-for benefit has been convincingly demonstrated and is of high magnitude, its low probability means that it has little effect on the harm-benefit balance.

Assessing the harms

All interventions expose the person directly concerned to the risk of adverse effects, and sometimes also pose a risk to their close contacts or a wider population (**c**). The incidence and severity of these adverse effects differ between individuals and interventions. Their evaluation is another step in the determination of the harm-benefit balance for a given patient (18).

A body of evidence. Clinical trials are not generally designed to study the adverse effects of interventions. Usually, because of the necessarily limited number of patients enrolled in clinical trials of limited duration, rare adverse effects are not identified, although occasionally some of them can be predicted from trial findings. For example, toxic hepatitis is foreseeable if elevated transaminase levels are frequently observed.

It is often necessary to wait years before the rare but serious adverse effects of an intervention are discovered, mainly through spontaneous reporting to pharmacovigilance centres by health professionals or patients (1,2,18).

However, various adverse effects are foreseeable, because they are related to the drug's mechanism of action and pharmacological properties (18). Examples include dry mouth caused by antimuscarinic drugs, and stomach pain caused by nonsteroidal anti-inflammatory drugs. These effects are often dose-dependent.

In practice, to determine the harms provoked by an intervention, it is important to incorporate the data from clinical trials into a body of knowledge, ▶▶

a- In this article, the term "intervention" refers to a treatment (pharmacological or otherwise), a diagnostic investigation, screening, or a general strategy that includes preventive, diagnostic or therapeutic measures.

b- In various situations, the anticipated benefit may also affect a wider population: for example, vaccination of young boys against rubella actually benefits the unborn children of women who may otherwise have contracted rubella during pregnancy (ref 43).

c- Withholding an intervention may have adverse effects, such as allowing a disease to develop, enabling transmission of infection to others, leading the person to erroneously believe that they are at no risk, etc.

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▶ including pharmacological knowledge, spontaneous reports of adverse effects, and the results of pharmacovigilance and pharmacoepidemiological studies.

Although each component of this body of data is often quite low-level evidence, together they can be used to determine the adverse effect profile of an intervention.

As a rule, less is known about the adverse effects of an intervention than about its benefits (18).

Take into account specific situations. Certain situations and patient characteristics increase the likelihood or severity of adverse effects (18). For example, when more drugs are co-prescribed, there is an increased risk that the patient will experience a drug interaction or confuse one drug with another (19). In elderly patients with dementia, neuro-leptics increase the mortality rate and the incidence of stroke (20). The adverse effects of drugs that are eliminated via the kidneys are more likely to occur in patients with renal impairment (18).

Age, pregnancy, current or past health problems, current or past treatments and their effects, the ease or difficulty with which the drug is administered, and the presence and cooperation of relatives are just some of the factors that need to be taken into account.

Beware of the risk of error. Errors can be committed throughout the care pathway, from prescriber to patient, and by everyone in between (pharmacist, nurse, etc.) (21). Several studies have shown that the incidence of medication errors is high, sometimes exceeding 50%. These errors are frequently linked to the organisation of care and drug packaging. For example, certain types of dosing devices (syringes, graduated measuring cups) can increase or reduce the likelihood of a dosing error (22-27).

A harm-benefit balance at a population level

Based on all of the evaluation data, including the benefits and the harms, the harm-benefit balance of a medical intervention is initially evaluated at population level.

This harm-benefit balance at a population level is the one generally used by regulatory authorities when considering whether to authorise or reject an intervention, by health insurance systems when considering whether to fund an intervention, and by certain organisations when considering whether or not to recommend the intervention (28). *Prescrire* for example evaluates the harm-benefit balance of preventive, screening, diagnostic and therapeutic interventions at a population level.

It is then up to each healthcare professional to draw on the conclusions published by the various sources, in order to determine the harm-benefit balance of the intervention for and with a given patient.

Conclusions are sometimes partly subjective. The organisations that establish the harm-benefit balance of an intervention at a population level sometimes interpret the same data differently and arrive at different conclusions (1,29).

First, evaluation of the harm-benefit balance of an intervention at a population level is a composite assessment. It takes into account the strength of the evidence for its efficacy and its harms, the type of benefit(s) and adverse effect(s) it produces, their magnitude, but also specific local or national characteristics.

Secondly, it often involves comparing effects that are very different qualitatively and in terms of their likelihood of occurring, based on levels of evidence that are also very different.

For example, to evaluate prostate cancer screening, one has to weigh a plausible but unproven decrease in the risk of dying from prostate cancer against a well-established and higher risk of erectile dysfunction following prostate surgery, an intervention that is more frequent in men who undergo screening (30). The conclusions drawn from the body of data depend on the weight given to each of these harms and benefits. It is important that organisations issuing recommendations and healthcare professionals take into account their own subjectivity and their own values to avoid drawing arbitrary conclusions on behalf of patients.

Nevertheless, the process of determining the harm-benefit balance becomes less subjective as more robust data become available.

The harm-benefit balance cannot be expressed as a value. Some working groups have tried to combine data on the efficacy and adverse effects of interventions, using mathematical models. The aim is to make the evaluation process explicit, and decision-making more reproducible, particularly decisions taken by regulatory agencies (31-34).

But expressing the harm-benefit balance of an intervention as a single numerical value would obscure the qualitative and partially subjective nature of the assessment process, giving the illusion that it is scientific, precise, and irrefutable (34).

It is also one of the reasons *Prescrire* has chosen to use the expression harm-benefit "balance" rather than "ratio". The term "ratio" suggests a scientific or mathematical parameter, while the word "balance" clearly highlights the fact that the assessment involves weighing the advantages against the drawbacks for each patient, with no preconceptions.

Sometimes biased? The harm-benefit balance determined at a population level, based on the available (published or unpublished) data, is subject to bias. Some pharmaceutical companies adopt a policy of only allowing the publication of research that presents their products in a favourable light, and of manipulating the scientific literature for commercial purposes (35-37). The results presented in published articles are sometimes massaged to overstate the benefits of treatment or to conceal serious adverse effects or even deaths (38,39). In addition, when choosing between articles of identical quality, medical journals are more likely publish articles that report positive results (40).

Ultimately, when the available data are biased, they are generally biased in favour of medical interventions, exaggerating their benefits and downplaying their harms.

A harm-benefit balance for each patient

Sometimes the harm-benefit balance of an intervention, determined at a population level, is so clearly positive that it would apply to nearly all patients. But in practice, it is rare for an intervention to have a favourable harm-benefit balance in everyone. Evaluation trials and studies often exclude populations such as children, pregnant women, older patients or patients with renal impairment (10,41,42). In most cases, there is very little information of direct relevance to an individual patient which takes into account the patient- and context-specific features that could affect the benefits and harms of an intervention.

In practice, to best assess the harm-benefit balance of an intervention for a patient, it is preferable to be familiar with their situation and way of life. Primary healthcare professionals are therefore in a better position to assess the harm-benefit balance than organisations, agencies or industry (28). A decision is made for and with a given patient, taking into account not only the evaluation data obtained on the medical interventions under consideration, at a population level, but also any relevant factors specific to the person or the context, especially

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medical and social factors. Be mindful too of the fact that healthcare professionals are liable to interpret evaluation data subjectively, and also the patient's needs and objectives.

Various factors to take into account. Many patient characteristics affect the assessment of the harm-benefit balance, in particular their medical history, current health problems and existing treatments, the risk of drug interactions, and treatment priorities. It is essential to take into account the patient's objectives, the importance they attach to the expected benefits and potential harms, their choices, personal values and lifestyle(1,9,18).

The harm-benefit balance also depends on the healthcare available, the knowledge and experience of the health professionals involved and their personal situation (tiredness, stress, degree of empathy with the patient, etc.) (1,3). Finally, the perception of the benefits and harms varies in complex ways between individuals, and over a given person's lifetime (13).

For example, an intervention liable to cause the joints of the little finger of the left hand to stiffen would have considerable implications for a violinist. Similarly, vitamin K antagonist therapy for atrial fibrillation does not have the same harm-benefit balance in a patient who is willing to undergo the regular laboratory tests this treatment requires as it does in a patient who lacks the motivation to adhere to this monitoring (1,7).

Involve the patient in determining the harm-benefit balance. There is a risk that healthcare professionals may project their own preferences and values on their patients to make decisions on their behalf. This in particular is why it is important to provide patients with clear and accurate information and to involve them in determining the harm-benefit balance of an intervention, with the aim of making a shared decision.

To achieve this, several aspects of a medical intervention should be addressed when discussing its potential benefits and harms with a patient:

– explain the nature of the health problem, its consequences and its natural history;

– analyse, along with patients, the objectives that matter to them, encouraging them to express themselves openly and to discuss any non-medical objectives they may have;

– present the various options in an unbiased fashion, including the option of no intervention;

– describe the possible consequences of these interventions, their advantages and drawbacks, explaining their nature, intensity, possible time course (onset, duration and reversibility) and the likelihood that they will occur, including any uncertainties;

– indicate how the benefits can be maximised and the harms prevented or minimised;

– explore with the patient how important all of these consequences are to him or her.

The harm-benefit balance may change

Assessing the harm-benefit balance of an intervention is a central part of clinical decision-making. It may also change. For each intervention, in each clinical situation, new scientific evidence accumulates over time. This includes information about the efficacy and adverse effects of the intervention, and about other possible options. Similarly, patients may also change over time: they age, they develop or recover from diseases, their treatments are modified, and their family or professional life, habits, wishes, values or priorities alter, etc.

Whether at the population or individual level, it is important to re-assess the harm-benefit balance of medical interventions periodically, in patients' best interests.

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