

Why is benefit-to-harm balance essential to treatment decisions?

The 1962 amendments to the U.S. Federal Food, Drug and Cosmetic Act require that for a new drug to be approved for marketing, there needs to be substantial evidence of both safety and efficacy when the drug is prescribed for its intended indication(s). In other words, a drug has to have beneficial effects that outweigh any potential harm; it has to have what is known as a favorable, or positive, benefit-to-harm balance. This is also true of other types of interventions such as medical devices and diagnostic procedures.

- WEIGHING BENEFIT VERSUS HARM REQUIRES A BALANCED SCALE.
- WHERE CAN I GET ONE?



What are the goals of treatment?

In general, there are three main goals of treating a patient:

- to make the patient feel better
- to reduce the risk of future disease complications
- to improve survival

There are those who include a fourth goal, “economic benefit,” both to the patient and to society, e.g., returning to work, supporting family, paying

taxes, reducing future demands on the healthcare system. Our view is that economic benefit represents a natural consequence of reaching one or more of the three main goals.

Although a particular treatment might be effective, it may not necessarily achieve all three goals. A painkiller or a drug for nausea might instantly improve a patient's well-being, but it would not be expected to bring any long-term benefit. In contrast, a drug to treat hypertension may reduce the long-term risks of cardiovascular complications and premature death without any tangible benefit to the patient, since most people with high blood pressure are asymptomatic. Some interventions may achieve all three goals. Effective antibiotic treatment of acute bacterial meningitis relieves symptoms, reduces the risk of neurologic complications, and decreases short-term mortality.

— THE GOAL OF THE TREATMENT
IS FOR YOU TO TAKE ONE PILL
THREE TIMES A DAY.



How is the benefit of a treatment documented?

Controlled clinical trials designed to determine whether a therapy prolongs life or reduces the risks of major non-fatal complications typically require thousands of study subjects treated for years. Diseases with very high complication rates or high mortality such as subarachnoidal hemorrhage or

pancreatic cancer are the exception. Except in these instances, evaluating whether a treatment reduces complications or improves survival takes a lot of time and is very costly. To document that a treatment provides symptomatic relief is less time-consuming and cheaper. For many chronic conditions, symptomatic improvement rather than clinical cure may be the most realistic goal and most prescription drugs are given with this intention. Difficulties associated with the assessment of symptoms are discussed in Chapter 11.

It is the responsibility of the manufacturer to document the value of a new product. Since a considerable investment of time and resources is needed to evaluate the effect of any treatment on survival or on the risks of disease complications, it is not surprising that there has been a lot of interest in biologic markers, or so-called surrogate endpoints. Evaluating the effect of various treatments on factors associated with the risk of disease, such as elevation of LDL cholesterol, systolic blood pressure and HbA_{1C}, has paid off handsomely for manufacturers. Several widely prescribed drugs have been approved for marketing based on a favorable effect on risk factors rather than definitive evidence of a true health benefit to patients. The value of these markers and the difficulties in drawing conclusions about their clinical utility based on treatment-induced changes are discussed in Chapters 13 and 19, respectively.

How is the harm of a treatment documented?

No treatment is free of adverse effects or harm. Any treatment decision ought to be based on weighing the likely favorable effects against the unfavorable ones.

A common complaint of patients is that a prescribed medication made him/her feel worse. The problem can range from something simple such as dryness of the mouth to serious adverse events that may require the treatment to be stopped. Even simple adverse effects can be very distressing for the patient, thereby reducing compliance. Adverse effects with a gradual onset are the most difficult to detect because the patient may not attribute them immediately to the treatment. Assessment of the patient's quality-of-life may sometimes help to detect modest changes in well-being due to the effects of a medication.

Occasionally, drugs may have serious adverse effects such as allergic reactions, hepatitis, cardiac arrhythmias and gastric ulcer. Despite this, attributing an adverse event to a specific treatment can sometimes be difficult, particularly when the event is rare, unexpected, or appears a long time after the start of treatment. It can also be difficult to recognize an adverse effect when it may occur as part of the natural history of the underlying condition. These challenges are discussed in Chapter 4.

Limited clinical experience with a drug when it is first marketed may result in it having a more “favorable” benefit-to-harm balance than it deserves. It has been estimated that as many as half of all new drugs have at least one serious adverse effect that is unknown at the time of drug approval.

Many drugs are metabolized in the liver and an emerging area of concern is the possibility of drug-drug interactions. Toxicity may occur when one drug inhibits the metabolism of another drug, or when two drugs compete for the same metabolic pathway. Of all the potential interactions, only those between

- DOC, ANY RISK OF SIDE EFFECTS WITH THIS DRUG?
- NONE THAT YOU DON'T ALREADY HAVE.



the most commonly prescribed drugs can be evaluated prior to marketing. In 1997, the FDA approved mibefradil (Posicor) for marketing in the U.S. The product was withdrawn within one year, after multiple serious drug interactions were documented, the most important one with simvastatin (Zocor).

There may also be other harmful effects of drugs that are less obvious. For example, some hormones, antibiotics and medications with prolonged half-lives may contribute to ecologic problems.

The high cost of an intervention may also be considered an adverse factor to patients and to society. Newer drugs with only incremental benefit are often much more expensive than older generic agents. “Patient labeling” can be an adverse effect of drug treatment itself. It has been reported that otherwise asymptomatic subjects who are placed on antihypertensive treatment develop various symptoms, since taking their medication serves as a reminder that they are not healthy.

Why off-label use of drug should be avoided?

One purpose of the important regulatory process of drug approval is to assure the public that approved drugs are both safe and efficacious. Randomized clinical trials represent essential tools in drug evaluation and they are usually required for regulatory approval. Manufacturers are only permitted to market drugs to health care providers and the public for the approved indication.

In contrast to the drug approval process, the practice of medicine is not regulated, so healthcare professionals can prescribe drugs for unapproved uses if they believe this is in the best interests of the patient. The pharmaceutical industry takes advantage of this through “indirect” marketing of its drugs for unapproved indications. This so-called “off-label” use is common. A study of 160 commonly prescribed drugs used among office-based physicians revealed that 21% of prescriptions were off-label.² There was little or no scientific support for most of these uses.

Limited evidence of safety and efficacy, including dosing, exposes patients to unnecessary risks. The direct risk is that the off-label use of the drug is ineffective, or harmful, or maybe both. The indirect risk is that proven alternative treatments, should they exist, may be denied. Since off-label use of

drugs is not evidence-based, it is generally to be discouraged. An exception may be in oncology, where it would be difficult to evaluate a chemotherapy agent in all tumor types and stages of disease prior to marketing.

In recent years, the government has attempted to regulate off-label promotion in response to subtle efforts by industry to conceal direct incentive payments to clinicians, questionable consultant contracts, and all-expense paid 'educational' trips. The alleged deceptive "off-label" marketing of gabapentin (Neurontin) was settled for \$468 million.¹ A more recent example is human growth hormone, which was never approved either to spur growth in children who were not hormone-deficient, or to slow the aging process in adults. Yet it has been widely prescribed for both indications.

Key Points

- 🔑 The value of a medical intervention is determined by its benefit-to-harm balance.
- 🔑 This balance may vary among patients with the same diagnosis.
- 🔑 Major treatment benefits range from symptomatic relief to prevention of disease complications to improved survival.
- 🔑 Safety information is often limited when a new intervention is introduced.
- 🔑 Early assessments of the benefit-to-harm balance tend to be overly optimistic.

"There are two sides to a coin"

Evaluating Clinical Research

All that glitters is not gold

Furberg, B.D.; Furberg, C.D.

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