

# 1B

# THERAPY AND HARM: AN INTRODUCTION

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Clinicians' most compelling questions involve choosing the optimal management strategy for their patients. For example, what are the benefits of prescribing pharmacologic treatment or mandating dietary change to lower blood pressure, cholesterol level, or a patient's weight. What are the benefits of screening women for breast cancer or screening men for prostate cancer, or of instituting a smoking cessation program? What symptomatic benefit or increased longevity might patients anticipate from treatment of their chronic heart failure, asthma, or diabetes? Equally important, what short-term or long-term adverse effects might they expect as a result of their intervention?

These questions address two related issues. First, what risks, if any, will result for patients if they smoke or are overweight, if their blood pressure, cholesterol level, or glucose level is elevated, or if their heart function is abnormal? These are issues of harm. Second, if we intervene to modify their behavior or their bodies' physiology, what benefits will ensue, and will these benefits outweigh any deleterious consequences? These are issues of therapy.

When we address questions of both therapy and harm, we are confronting issues of causation. There are myriad examples. In a particular group of people (healthy men or women, patients with diabetes, or patients with heart failure, for example) is there a causal relationship between an exposure (smoking, obesity, or high blood pressure) or intervention (an antismoking or weight loss program, or a drug that lowers blood pressure) and a particular anticipated outcome (lung cancer, myocardial infarction, or stroke) or unanticipated outcome (eg, the profound visual loss resulting from one antihypertensive medication<sup>1</sup>).

For each of these questions, there is an underlying true answer. If our inferences about the underlying truth are wrong, the consequences may be disastrous. Consider how many lives must have been lost over the course of several hundred years when physicians were convinced that blood-letting was an effective treatment for an extraordinarily wide variety of illnesses. It is impossible to estimate the numbers. By contrast, records of the number of prescriptions and an evaluation of the magnitude of harm from a randomized trial make it possible to estimate the thousands of lives lost resulting from the much more recent administration of class I antiarrhythmia drugs—agents that physicians believed would prevent lethal arrhythmias when, in fact, they were causing them.<sup>2</sup>

Why has the medical community made such disastrous blunders, and what can we do to prevent their repetition? The answer lies in clinicians learning rules of evidence that allow them to differentiate false claims from valid ones. If you are content with a practical approach to determining when you can believe study results and when you cannot, read on. If, however, you would like a deeper conceptual understanding of the foundation of our *Users' Guides to the Medical Literature*, turn now to Part 2B, "Therapy and Harm, Why Study Results Mislead: Bias and Random Error."

## THREE STEPS IN USING AN ARTICLE FROM THE MEDICAL LITERATURE

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When using the medical literature to answer a clinical question, approach the study using three discrete steps.

In the first step, ask, “**Are the results of the study valid?**” This question has to do with the believability or credibility of the results. In answering this question, you consider whether the estimate of the treatment effect reported in the article faithfully represents the direction and magnitude of the underlying true effect. Another way to state this question is: “Do these results represent an unbiased estimate of the treatment effect, or have they been influenced in some systematic fashion to lead to a false conclusion?” If the results are valid and the study likely yields an unbiased assessment of the treatment effect, then the results are worth examining further.

In the second step, ask, “**What are the results?**” to consider the size and precision of the treatment’s effect. The best estimate of that effect will be the study findings themselves; the precision of the estimate may be superior in larger studies.

Once you understand the results, ask yourself the third question, “**How can I apply these results to patient care?**” This question has two parts. First, can you generalize (or, to put it another way, particularize) the results to your patient? For instance, you should hesitate to institute a treatment if your patient is too dissimilar from those who participated in the trial. Second, if the results are generalizable to your patient, what is the net impact of the treatment? Have the investigators measured all outcomes of importance to patients? The impact depends on both benefits and risks (side effects and toxicity) of treatment and the consequences of withholding treatment. Thus, even therapy that is effective might be withheld when a patient’s prognosis is already good without treatment, especially when the treatment is accompanied by important side effects and toxicity.

## THERAPY AND HARM: STUDY DESIGNS

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### Randomized Controlled Trials to Assess Treatment

When investigating an issue of treatment, researchers have much more control than when exploring a question of harm. For instance, they can determine who receives the experimental intervention and who receives the control (eg, no treatment or placebo). Ideally, they will allocate patients to groups according to a process analogous to a coin flip, called *randomization*, and they will conduct a randomized controlled trial. In addition, they can design their study so that neither patients nor caregivers are aware of which patients receive the experimental treatment.



## Observational Studies to Assess Harm

By contrast, researchers looking at issues of harm generally do not have this sort of control. They cannot dictate to people whether they should live in high- or low-pollution environments; neither can they allocate them to groups living in spacious or overcrowded settings. Investigators cannot conceal from study participants their living environment—or whether or not they smoke. As a result, investigators use observational study designs. They may follow patients who, as a result of preference or circumstances, have been exposed to a harmful stimulus. They follow them forward in time to determine if they suffer the outcome about which they are concerned, the target outcome (a *cohort study*). Alternatively, researchers may select individuals who have already suffered the target outcome. In addition, they select another group that has not yet suffered the target outcome, and compare the extent to which the two groups had been exposed to the putative harmful agent (a *case-control study*) (see Part 1B2, “Harm”).

## Applying Appropriate Criteria

Inferences from studies investigating harm are generally much weaker than those from studies of therapy. As a user of the medical literature, you must apply different criteria to a study of a therapeutic question than to one investigating a harmful exposure. We therefore provide separate *Users' Guides* for coverage of issues of therapy and harm (see Part 1B1, “Therapy,” and Part 1B2, “Harm”).

There are exceptions to this general rule. Sometimes, the harmful exposure may be a medical intervention, such as a drug, and researchers will perceive the putative harmful effect as occurring quickly and frequently. Under these circumstances, investigators may be able to use the study design usually associated with therapy to determine if there is a causal relation between the drug and the toxic effect.

Similarly, there may be no randomized trials available—or even feasible—addressing a particular therapeutic issue. Investigations of rare conditions, community interventions, the care delivered in different hospitals (see Part 2B, “Therapy and Harm, Outcomes of Health Services”), or the quality of care within a hospital (see Part 2F, “Moving From Evidence to Action, Clinical Utilization Review”) do not easily lend themselves to randomized trials. Randomizing health care systems to rely more on primary care physicians or specialists, or to base reimbursement on fee-for-service or capitation, or to public funding vs user-pay, seems, for the foreseeable future at least, improbable.

In all situations when clinicians addressing issues of therapy find that randomized trials are unavailable, they need to rely on cohort and case-control studies—the strongest evidence available. In doing so, they must apply the appropriate criteria for the evaluation of these studies, criteria that ordinarily would be associated with investigations of potentially harmful exposures. When relying on cohort or case-control studies to address issues of therapeutic benefit, however, clinicians must bear in mind that the strength of any inferences about the causal relation between the intervention and the outcome become much weaker than they would if evidence came from a randomized trial.

## References

1. Wright P. Untoward effects associated with practolol administration: oculomucocutaneous syndrome. *BMJ*. 1975;1:595-598.
2. Moore TJ. *Deadly Medicine*. New York, NY: Simon & Schuster; 1995.