Number Needed to Treat (NNT); Number Needed to Harm (NNH)

Problems in diagnosis arise daily. We understand what we mean when we say, “I think you have disease X.” We often don’t know for sure, as in diagnosing Alzheimer’s or Parkinson’s diseases (PD), and we understand that we have a certain degree of confidence in being correct. “I’m sure you have disease X; I’m pretty sure; I think you might…” We are less clear, I think, in how we classify the efficacy of our treatments. When we treat infections we expect cure in 100% of our patients, and failing this, we blame the organism for being resistant, the patient for not taking their medication properly or having an anatomic or immunologic disorder. But this is not true for the chronic ailments that afflict 75% of the elderly. We don’t treat hypertension because it is causing symptoms. It is the “silent killer.” It is treated to prevent problems, namely heart attack, stroke, kidney failure and atherosclerotic disease, and the secondary problems each of these may then cause. Yet our drugs are not 100% effective even when they are “successful,” since we confuse treating a risk factor for the disease with the disease itself. We reduce the likelihood of impending stroke and heart attack when we lower blood pressure. We do not prevent all strokes or heart attacks. We can be 100% confident that we reduced the blood pressure, but that doesn’t translate into improved health for the vast majority of the treated patients since they are not going on to have strokes or heart attacks. By treating them they are not “getting better.” They are “not getting worse.”

A large percentage of our contemporary treatments are intended to reduce risk, not treat symptoms. An operation for a pinched nerve solves a problem, whereas a carotid endarterectomy is intended to prevent one. Treating diabetes controls blood sugar and therefore the problems of hypoglycemia (confusion, seizures, coma) and hyperglycemia (confusion, seizures, polyuria, polydipsia, weight loss, stroke-like symptoms) and may possibly reduce some of the long term complications. When we treat Parkinson’s or Alzheimer’s diseases, we are treating symptoms, and not altering the pathological process of the disease itself. We can tell if these drugs “work” because the symptoms improve.

Complicating our concept of treatment-prophylaxis is the problem of identifying suitable “biomarkers,” which are clearly defined metrics of the disease’s severity. How well does a medicine control pain, as measured by an accepted pain scale? Does it reduce total pain? Does it control motor function in PD as measured by some accepted scale? But in the case of cholesterol, which is not a symptomatic disorder but a “biomarker” of increased risk of vascular disease, we found that simply lowering it, which a recent drug did quite significantly, led to no decrease in the risk of heart disease or stroke, much like getting rid of the smoke, but not the fire.

I recently attended a stimulating lecture on the drug treatment of refractory depression. Once he got over the problem of defining “refractory,” the speaker introduced the concept of “number needed to treat” and “number needed to harm,” which was a foreign concept to several in the audience. It’s a valid and sometimes useful way to estimate treatment effect. It is helpful for estimating efficacy for prophylactic and treatment therapies, especially when taking cost into account. For example treating systolic blood pressures above 160 in the elderly, one needs to treat 120 people to prevent one stroke in a year. Carotid endarterectomies performed by highly competent surgeons must be performed on 40 arteries to prevent one stroke per year in patients with asymptomatic stenosis. Clopidogrel is mildly better at reducing stroke risk than aspirin but 250 people need to take the drug in place of aspirin to prevent a single stroke per year, at about 150 times the price.

In psychiatric trials the numbers are interesting because we think of treating disorders like depression as we treat an infection, try one medication, titrate the dose, then if not successful, try another drug. Yet a very good result for treating depression may have an NNT of 3-5, which means that only 20-30% of treated patients are improved by drug, a ratio that would not inspire confidence in most of us, although this is in addition to the benefit of placebo. And this NNT, which is fairly typical for psychiatric treatments, compares favorably with the outcomes for common medical treatments.

Should we be telling patients that our drugs are effective 30% of the time or less? Do we really expect this result, which, I suspect most readers will find uncomfortably poor, when we prescribe or take a new drug, or do we expect that most of our patients will improve? I note, in passing, that the results of double-blind trials and “real life” are quite different, with the placebo effect of the doctor giving a known “effective” treatment, versus the measured placebo effect of simply participating in a drug trial. I assume that the former is the more potent, but perhaps not.

We can stand things on their heads and calculate the “number needed to harm,” which is a measure of side effects. How many subjects are treated before causing an iatrogenic complication? This is a less useful number because the potential side-effects are considerably larger and often less well-defined than the precisely defined treatment effect. Death, however, is a rather well-defined outcome and there is no universally acceptable ratio to establish a certain benefit to counter-balance the risk of death in a minute percentage of the population. The extremely small increase in death rate for people taking atypical antipsychotics earned those drugs a “black box” warning by the FDA, which made the drugs harder to use.

The NNT can be used to calculate financial outcomes. If it costs a certain
Contagion as a Fiscal Problem

AN ALLEGEDLY NEW COMMUNICABLE DISEASE ENTERS OUR IMMEDIATE COMMUNITY. We hear about it—cloaked in frightening metaphors—in the local newspaper and its existence is verified in the other publications within the state. Learned commentators then remind us of the mayhem wrought by prior pestilences and pandemics; and both our wise statesmen and clergy admonish us, perhaps urging a day of fasting and repentance, to prepare us for the worst.

Important questions necessarily arise: Is this an utterly new pestilence or merely a recurrence, such as influenza, of an infectious disease that has repeatedly arisen amongst humans in the past? Is the infection confined to humans, such as poliomyelitis, or does it transcend species barriers, such as with influenza, and concurrently infect swine, birds or other creatures?

We will assume now that this newly arisen pestilence affects both children and adults indiscriminately, is suppressed by no known antibiotic and results in a relatively high mortality rate. A local committee is then assembled to determine what the community might do. Their decision might be: (1) to do nothing beyond the customary use of private medical offices, clinics and emergency rooms; or (2) to appeal to the citizenry to participate in specified days of prayer, sacrifice, humiliation and fasting; or, (3) to encourage the civic leadership to proactively invest in known preventive measures and community-wide educational interventions.

The decision is not a simple one: Community priorities must be examined. The past experience of other communities must be explored. And certainly a set of fundamental questions will demand answers before tangible steps will be taken.

- Is there certainty that the disease is communicable; that is, caused by a living organism such as a virus, a bacterium or a fungus? If communicable, how is it communicated? By air, by drinking water? By physical contact (including venereal intimacy)? Or by the intermediacy of an insect such as a mosquito or tick?
- Have neighboring communities been similarly affected? And if not, have they been duly warned of the nature/characteristics of this new ailment?
- Has the United States Public Health agencies, particularly the Centers for Disease Control & Prevention, been appropriately notified and their active assistance requested, including their superb laboratory facilities and mobile epidemiologists?
- Is the disease of sufficient economic and social importance—for this community—to justify a formal preventive medicine campaign?
- Is there the political will to use public moneys to confront the epidemic? The United States, in the 1920’s and 1930’s was confronted with a near epidemic of venereal disease, particularly syphilis and gonorrhea. Many religious communities were strenuously opposed to any federal anti-syphilis program, contending that the core disorder was sinful behavior and hence not in the domain of public health and certainly not within the realm of federal responsibilities. By the mid-1930’s, a cautious public education program was instituted with posters in public bathrooms declaring: “Stamp Out Venereal Disease!” as well as an earnest program in the armed forces to combat venereal disease.
- Are there religious scruples that might cause sufficient numbers to resist the contemplated preventive medicine interventions (e.g., a recommendation for the use of condoms)? Or secular worries that vaccines might cause autism?
- Are there medical interventions (such as enhanced water purification methods or enforceable quarantines or vaccines) which have been shown elsewhere to be medically proven and cost effective for this particular pestilence?
- Do any of the preventive measures, such as a contemplated vaccine, carry significant morbidities and complications? (As an example, the original, crude Pasteur vaccine to combat rabies, devised in the late 19th Century, was clearly effective medically but its use carried a high frequency of serious, and sometimes fatal, neurological complications.) In the sphere of public health, there are no free lunches.

A communicable disease—whether it be new or recurrent—poses many challenges and choices for the affected community. Ultimately, of course, it resolves itself to a mixture of competing

Disclosure of Financial Interests

Lectures: Teva, Ingelheim Boehringer; General Electric
Consulting: United Biosource; Bubaloo, Halsted, Reitman LLC; EMD Serono; Genzyme; Teva; Acadia; Addex Pharm; Schwarz Pharma
Research: MJFox; NIH: Cephalon; EMD Serono; Teva; Acadia
Royalties: Demos Press

Correspondence

e-mail: joseph_friedman@brown.edu