Personalized medicine- Does it Matter?

Louis R Caplan MD

Professor of Neurology Harvard Medical School

Senior Neurologist, Beth Israel Deaconess Medical Center Boston

Palmer 127, West Campus

Beth Israel Deaconess Medical Center

330 Brookline Ave

Boston 02215, Massachusetts, USA

Office phone- 617-632-8911

FAX-617-632-8920

lcaplan@bidmc.harvard.edu

Neurology has been called the queen of clinical disciplines. The relationship between doctor and patient is extremely complex and multifaceted. Like any successful clinician, the neurologist must pay attention to the person and the environment to manage illness. Neurologists have been trained for generations to test their clinical hypotheses by performing detailed histories and neurological examinations to arrive at a complete differential diagnosis. Additional investigations and imaging narrow the diagnosis to those pertinent to that patient. Choosing treatment considers the benefits and risks of each potential treatment for that complex individual. It is of course necessary to know quite a bit about the patient and his or her social milieu and psychological make-up. This approach can be characterized as *personalized medicine* since it emphasizes the medical and personal details of each individual. This system is the backbone of a monograph entitled The *Effective Clinical Neurologist* by Joshua Hollander and me, now in its third edition.[1]

Recently, there has been a major thrust to demand that all treatments become "evidence-based." The highest level of *evidence* is derived from randomized therapeutic trials that consider treatments rendered to large groups of patients with general diagnoses

(for example; transient ischemic attacks (TIAs) and minor strokes, multiple sclerosis, traumatic brain injury etc). This approach is best suited to choosing treatments for the large bulk of patients with a general condition and so can be characterized as *group medicine*.

Doctors care for one patient at a time and must consider: 1) the patient's medical problem, and 2) the patient's risks for disease, and 3) the patient, their background, genetics, socio-economic milieu, psychology, responsibilities, goals etc, and 4) the benefits and risks of potential therapeutic strategies to treat the patient's conditions (often multiple) and to prevent conditions that they are at risk for developing. The effective physician must communicate with the patient and often family members and friends, listening and teaching. These functions are extensive and difficult. All this requires much innate intelligence, experience, sensitivity, and training. And it takes time, a commodity now often jeopardized by large patient lists, managed care directives, and the need to support oneself and one's family. *Evidence-based medicine* relates mainly to one of these doctor functions, assessing the scientific evidence for various treatments.

What is "Evidence-based medicine"?

The latest medical crusade is to render the care of patients *evidence-based*. This term has become a shibboleth, a sacrosanct icon almost like motherhood. Who could possibly be against basing decisions on evidence? The Oxford College Dictionary defines evidence as "something that furnishes proof; an outward sign; an indication, testimony". Haven't doctors always prided themselves in having some evidence behind treatment selection? It is difficult to think of a polite term for actions and decisions based on no evidence. The change from the past, however, is that advocates of evidence-based medicine have established a clear unambiguous requirement for what they consider credible evidence – the randomized controlled trial and especially the systematic review of several randomized controlled trials. The almost religious zeal for placing all decisions about patient care under the banner of evidence-based misses the real problem: that is, how well does the evidence from trials apply to the care of individual patients?

In contrast to the situation envisioned by evidence-based medicine zealots, courts of law accept and evaluate many different types of "evidence" and testimony. Judicial

decisions depend on how the evidence applies to the individual case being considered. Governmental organizations, insurance companies and other funders embrace this new concept of evidence-based medicine since few treatments meet the strict criteria. They would prefer not to pay. He who pays the piper calls the tune.

How do trial data relate to treating individual patients? Do randomized trials have theoretical and practical limitations?

Physicians in the free world are not compelled to give all patients with a condition the same defined treatment, as is the case in trials. Randomized trials mandate that numbers of patients with a general condition will be given treatment X and the results will be compared with patients given treatment Y or Z or placebo.

Trials, the core of evidence-based medicine, have important theoretical and practical limitations. They are expensive, time consuming, and require enormous resources. To provide statistically valid results, randomized trials must contain *large numbers of patients* with enough end points for analysis. Sufficient end points must be obtained in a relatively short period. The condition studied must either be acute and cause adverse end points or rapid improvement within a short time. Chronic conditions must be severe enough to cause clear end points within 1-5 years of follow up. Many medical conditions are unsuitable for study by trials. Less common, heterogeneous, and chronic conditions are difficult to study in trials. Patients who are too ill, too old, too young, female and "of childbearing age," incapable of giving informed consent, too complex, or too full of coexisting illnesses are often not included in trials. But these are just the patients who visit doctors in their office and are under their care in the hospital.

The major theoretical limitation of trials is the issue of *numbers vs specificity*. For trials to yield statistically valid results, they must include many patients - *numbers*. For the results to be useful to practicing physicians, the data must *specifically* apply to individual patients with the condition studied. To include enough patients, the condition to be studied must be common and usually multiple physicians at multiple centers must be used. A single doctor or medical centre would have too few patients or would take an unacceptably long time to accrue the number of patients needed. To achieve numbers, a

lumping strategy must predominate over *splitting*. For example, to study the effectiveness of a treatment to prevent embolism in patients with mitral valve prolapse, a study would not be able to obtain enough patients with mitral valve prolapse, mitral regurgitation, and mitral valve fibrinoid degeneration who had prior brain or systemic emboli and congestive heart failure even though this group is at highest risk and would be most likely to respond to prophylaxis. The study would have to include all patients with mitral valve prolapse to recruit enough patients.

The sample size of a trial will increase if: the projected effectiveness of the treatment (the percentage reduction in adverse outcomes) is low (10-15%); a number of treatments will be studied; the follow-up period is short, many patients will be lost to follow-up, withdraw, or become non-compliant; the anticipated outcome event rate is low; and a high power of protection from type I and type II errors is desired. As an example of the extraordinary numbers of patients needed for some studies, the authors of a meta-analysis of randomized controlled trials of agents that decrease platelet aggregation for the secondary prevention of stroke calculated that 13,000 patients would be needed to detect with 90% power, an observed reduction in endpoints of 15% with aspirin.

The greater the numbers of patients needed, the more pressure there is to adopt a lumping strategy. The more a study lumps diverse subgroups, the more *general* are the results and their applicability to specific patients declines. For practicing physicians, treatment must be very specific. Physicians are faced with individual patients for whom they must make therapeutic decisions. **To be useful, trial results must help physicians treat individual patients in given situations.** Subgroups of patients can be managed by prospective stratification, that is, by randomizing patients using predetermined criteria (e.g., sex, race, age) to ensure that subgroups will be relatively equally represented in the different treatment groups, or by analyzing the treatment results by subgroup determinants that have been prospectively defined. But the subgroups must also be very large to satisfy statisticians.

A confounding issue is the number of treatment and agents that patients receive. For example, many trials consider secondary stroke prevention after an initial TIA or stroke. Patients are enrolled even 3 to 6 months after their initial cerebrovascular event.

These trials have not taken into consideration the effect of the initial treatment before randomization on the outcome. Experience and outcome data show that treatments that are effective during the initial event (e.g. thrombolytics, mechanical clot extraction, anticoagulants, antiplatelets) often have durability and greatly impact the occurrence of later events. If initial treatments are taken into consideration a much larger number of patients would be required to assess the results. Similarly many patients with vascular disease are treated with polypharmacy prior to enrollment. It is difficult to balance the control and various treatment groups against all potential drugs and combinations of drugs.

There are also many practical problems confronting trialists. Trials are big operations. Multiple centers require many physicians and clerical staff. Computer hardware and software and statistical skills are needed to record, manage, interpret, and analyze data. The personnel and equipment are very costly. Money for *funding* comes either from governmental, or private sources, most often pharmaceutical or device companies. Much time and effort is expended in writing grants and much pilot data are required. Government funding is becoming scarcer all over the world. Alternatively, private industry may be interested in funding grants if their products are being studied. Potential problems arise from involvement of private enterprises that have much to gain and much to lose, depending on trial results. Many companies strive to dictate trial methodology and/or play a role in analysis and publication of the results as a condition for funding. Companies have bailed out of studies depending on company finances and goals. Many worthwhile trials go unfunded.

Inclusion and exclusion criteria are designed so that patients entered will be *pure breed* and can be followed until study completion. Most severe intercurrent diseases exclude patients as do relative contraindications to treatments studied. Comorbid conditions such as alcoholism, cancer, liver, lung, blood, and renal disease are exclusions. The plethora of exclusions often makes it difficult to recruit enough patients to meet sample size requirements. Estimates of the number of patients a centre predicts it will recruit are usually at least 2-3 times more than they actually manage to enter once the trial begins. In some trials, patients who are eligible under the inclusion/exclusion rules

of a trial are not entered by physicians who feel that a particular patient needs the treatment and should not be randomized.

Eligible patients are not always easy to enroll in trials. Many patients decline because they don't want to be *guinea pigs* and view trials as something others do, especially *charity cases*. Some patients are put off by the acknowledged lack of a scientific basis for treatment and cannot accept that a *flip of the coin* will decide treatment. Some are disturbed that neither they nor their physicians will know what treatment they receive. Especially disconcerting for many is the prospect that they may receive a placebo. They believe their problem is serious and warrants active treatment. With time and patience, some of these patients can be enrolled but with much effort. Alas, some who have enrolled will be dissuaded later by their all-knowing friend or relative, and will drop out. To document that all procedures have been followed and all necessary exams and evaluations have been performed, most studies require mountains of paper. Completion of forms takes time. Often, the filling out of forms is delegated to a clerk, a resident, or the most junior investigator. The validity of the data is thus jeopardized. The results are only valid if the data are reliable and accurate. Senior experienced clinicians should have seen all patients and personally reviewed the forms to ensure accuracy but this is often not done.

To compare the effectiveness of different treatments, outcomes must be measured and quantified. Trials that study stroke prevention are an example. This is simple if large events such as death or new stroke are used, but are all strokes equal? In nonfatal diseases, other criteria e.g. severity of deficits, disability, or other *objective* measures must be used. Especially in neurology, severity and disability scores are problematic. How can aphasia be compared with diplopia, ataxia, facial numbness, and limb weakness? How are weights assigned to various abnormalities? For some patients, a hemianopia that makes reading difficult but does not effect daily living poses no major problem but to a physician, editor, or surveyor the same deficit is devastating.

Are some recommendations based on trial results useful?

Randomized trials that study common, relatively homogeneous, specific, acute conditions have been quite helpful to practicing physicians. A randomized trial of high concentration oxygen therapy given to premature infants showed that blindness due to retrolental fibroplasia was an important complication of this treatment. The results prevented innumerable cases of blindness. Before this trial, renowned pediatric professors had embraced this treatment. Many trials and analyses clarified the indications for carotid artery surgery in symptomatic patients with various severities of arterial narrowing. Many trials and analyses have shown that warfarin anticoagulation is superior to aspirin and placebo treatment in preventing strokes in patients with atrial fibrillation. Cardiac revascularization conveys more frequent and better survival from cardiac shock than medical stabilization. There are many such examples of very useful trials that have promoted changes in treatment of patients. The Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial showed that monitoring of medical therapy especially physical activity, nutrition, and weight were extremely important in those patients assigned to medical therapy. This result changed the way medical therapy will be used in subsequent stroke trials.

Are other trial-based guidelines and recommendations less useful?

Some other randomized trial results are much less useful to practicing physicians. In this category are the stroke prevention trials of drugs that decrease platelet aggregation. Some studies showed in full group analyses a benefit for aspirin, aspirin combined with sulfinpyrazone or dipyridamole, ticlopidine, and clopidogrel. Unfortunately, the mixture of patients treated with antiplatelet aggregants or placebo was probably not representative of patients in the community presenting with TIAs or minor strokes. In none of these studies was clarification of the nature and severity of the causative vascular and cardiac lesions required for entry. Patients with lesions thought favorable for carotid surgery were often operated on and were ineligible. Patients with "surgical" lesions deemed unfit for surgery- and those unfit for angiography were included in medical treatment groups. Some patients with detected cardiac sources of

emboli were not entered. No systematic evaluation for carotid artery or cardiac disease was mandated. Subgroup analysis was only by sex and tempo of ischemia (TIA, reversible ischemic neurological deficits, minor stroke). The tempo of ischemia does not predict the nature, severity, or location of causative vascular lesions. Since cardiac studies were not required, the groups must also have contained patients with cardiac-origin brain embolism as the cause of their brain ischemia. A meta-analysis of randomized control trials of antiplatelet agents in the secondary prevention of stroke found that for aspirin compared with placebo there was a statistically nonsignificant reduction in stroke of 15% and a trend in reduction of stroke for any regimen containing aspirin. The results of these studies are difficult for physicians to apply to individual stroke patients with identified stroke mechanisms e.g stenosis of the vertebral artery, arterial dissection, fibromuscular dysplasia, cardiogenic embolism. In defense of the studies cited, the technology available now were not widely available when the studies were designed. To recruit enough patients, the decision was made not to require angiography for entry (the numbers versus specificity issue). The result is that the data, despite enormous expense, are not very useful for physicians treating patients with the conditions studied in the trials. Future trials of antiplatelet aggregants should be conceived differently and have sufficient subgroup data related to the presence and severity of vascular lesions to be meaningful to practicing physicians.

Guidelines for thrombolysis in acute stroke patients are still largely based on a single government funded study planned 25 years ago and published 20 years ago. Release of the results of the National Institute of Neurological Diseases and Stroke (NINDS) trial gave momentum to a movement quickly to introduce intravenous thrombolysis widely into the community. During the summer of 1996, about 6 months after the publication of the NINDS trial, the FDA in the USA approved the use of rt-PA for the treatment of stroke patients when the drug was given within the first 3 hours. The NINDS trial did not include patients treated after 3 hours. The American Heart Association and American Academy of Neurology published treatment guidelines that recommended intravenous administration of rt-PA according to the NINDS protocol. The recommendations suggested that a CT scan performed before thrombolysis should not show major infarction, mass effect, edema, or haemorrhage. The guidelines did not

require or suggest MRI or vascular tests before treatment, despite the fact that stroke is a vascular disease. The inclusions and exclusions of the NINDS trial were copied in the recommendation. Patients who had minor deficits, were improving, awakened with deficits, or had seizures were not recommended for IV thrombolysis. The recommendations have never been fully updated.

Before and after the NINDS trial, many thousands of patients have been given stroke thrombolyis throughout the world. Early studies involved angiography before and after intravenous or intra-arterial thrombolysis. These studies and recent studies using CT and MR angiography showed convincingly that outcome correlated highly and consistently with opening of arterial occlusions and reperfusion. Many patients treated after 3 hours improve after thrombolysis, depending on the presence and amount of brain infarction, the nature and location of the arterial occlusion and the clot burden, and the presence and amount of collateral circulation. Recently, clot retrieval devices, have ben shown to improve outcomes after IV rt-PA in selected patients with intracranial arterial occlusions who have no or small regions of brain infarction.

Many patients now excluded from thrombolysis could potentially benefit. Many who awaken with deficits or in whom time of onset is unclear can be studied using modern brain and vascular imaging to determine the potential salvagibility of brain tissue by thrombolysis. Patients with minor or improving deficits frequently worsen or crash in the ensuing 24 hours after onset. Some patients with seizures have acute vascular occlusions as the cause. Modern brain and vascular imaging can be done safely and quickly and can yield the key information needed logically to choose those patients who are likely to benefit from thrombolysis, those who are likely to be harmed, and the best route of administration of the agent or the potential of device-engendered reperfusion.

The present thrombolytic recommendations need to be redone completely. The new guidelines should be based on what has been learned in the quarter century since the NINDS trial. The present guidelines are very time-based. Following them prevents many potentially eligible patients from being treated. They expose other patients who do not have occlusive arterial lesions to needless risks. Less than 10 percent of potentially eligible acute stroke patients are given thrombolysis. It should be obvious to even the most naïve person that patients do not change from good candidates (queens) to no

candidate (pumpkins) when the clock strikes four thirty. Use of a clock and a plain CT scan to screen candidates in 2016 is archaic and is completely outmoded except in very peripheral rural regions where skills and technological equipment are lacking. Organizations have failed to up-date the currently outmoded recommendations until now because the important information (evidence) gleaned from decades of experience is not "evidence-based" according to their very strict criteria.

Conclusions

We need more and better randomized therapeutic trials designed by clinicians to answer clinically relevant specific therapeutic problems. We need more critical reviews of trials and therapeutic dilemmas by experienced senior clinicians. Inexpert reviews by young academics often miss nuances and frequently lack clinical perspective and experience. All available information, not just that gleaned from randomized trials, should be included.

The panacea and savior for medical therapeutics is not, and will not be randomized trials or evidence-based reviews or meta-analyses. There are too many situations that cannot be clarified by trials. In other conditions general results are hard to apply to complex patients. Some envisage that the bulk of medical care will be delivered by primary care physicians who will spend much time at the computer reviewing evidence-bases to guide therapeutic decisions. The role of specialists who have extensive experience and training in treating patients within their fields of expertise is minimized. After all, specialists are thought to be more expensive than primary care physicians (although no credible data proves this assumption). What a nightmare for present patients and for doctors who ultimately will also become patients. Instead, I suggest that more time should be spent by general physicians and specialists at the bedside and in the clinic finding out exactly what is wrong with each patient, and getting to know each patient and their circumstances, family situations, psychosocial and economic stresses, thoughts, fears, biases, and wishes. Therapeutic decisions are made with, by, and for complex individuals. They cannot be readily homogenized without losing the essence of what being a doctor is all about.

Summary

Proponents of *evidence-based medicine* have established a clear unambiguous requirement for what they consider credible evidence – the randomized controlled trial and especially the systematic review of several randomized controlled trials. They propose that clinical practice should be dominated by adherence to the "evidence.," as they define it.

Taking care of complex patients is very different from care during trials. Many conditions are unsuitable for trials. Many patients are not included in trials. Patients selected are often not representative of the conditions seen in the clinic by practitioners. There are important limitations in trial design and analysis that make the "evidence" not very practically useful in everyday practice. Instead of basing decisions largely on trial results of homogenized groups of patients, I advocate spending more time at the bedside and in the clinic finding out exactly what is wrong with each patient, and getting to know each patient and their circumstances, family situations, psychosocial and economic stresses, thoughts, fears, biases, and wishes. Therapeutic decisions are made with, by, and for complex individuals. Therapeutic decisions should be guided by detailed knowledge of the pathology, pathophysiology, and circumstances in individual patients. One size does not fit all or most patients.

George Thibault said it very well: "We then need to decide which approach in our large therapeutic armamentarium will be most appropriate in a particular patient, with a particular stage of disease and particular coexisting conditions, and at a particular age. Even when randomized clinical trials have been performed (which is true for only a small number of clinical problems), they will often not answer this question specifically for the patient sitting in front of us in the office or lying in the hospital bed." (Thibaud, 1993).

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