EVIDENCE-BASED MEDICINE

Evidence-Based Medicine: Past, Present, and Future

Gordon Guyatt, MD, MSc

ABSTRACT

Evidence-based medicine (EBM) offers clinicians and patients approaches to optimal use of the medical literature in solving patients' problems. The best evidence for EBM comes from examples of how traditional decision-making approaches have gone wrong, and how evidence-based approaches can remedy the problems. Thought regarding the nature of EBM has evolved, and now focuses on two elements. First, EBM posits a hierarchy of evidence. Second, EBM emphasizes that evidence is never sufficient for making decisions, which always requires consideration of values and preferences. Efficiently integrating patients' values and preferences into individual decision-making represents the most interesting challenge facing EBM.

In this article, I will briefly describe what I mean by evidence-based medicine (EBM), discuss the evidence regarding the impact of EBM, describe advances in our thinking about EBM over the 12 years since the term first appeared in the published literature,[1] and present challenges that face EBM. I borrow extensively from my prior writings on this topic, in particular from material that interested readers can find in our Users' Guides to the Medical Literature.[2]

WHAT IS EVIDENCE-BASED MEDICINE?

Evidence-based medicine (EBM) differs from prior approaches to medical practice in several important ways. It puts a greater emphasis on using published literature to solve medical problems, posits an explicit hierarchy of evidence, suggests specific guidelines for the interpretation of evidence from the medical literature, and offers an approach to resolve medical problems that explicitly acknowledges the role of patient values and preferences. I am not suggesting that all of these elements were not, to varying degrees, part of conventional medical practice. Nor am I suggesting that they have been absent from the writings of various authors, both ancient and recent, prior to 1990. EBM does, however, represent an important change in emphasis and, increasingly, a systematic approach to clinical problem-solving.

WHAT IS THE EVIDENCE SUPPORTING EVIDENCE-BASED MEDICINE?

Medical practice is intended to allow patients to live longer and improve their quality of life. The ultimate test of EBM would therefore be a trial in which medical students would be randomized to conventional or EBM training and followed for a few years subsequent to graduation, while monitoring the outcomes of their patients. Such a trial is, for a host of reasons, not feasible.

The dictates of EBM suggest that when the ideal study is not available, one falls back on the strongest evidence that one can access. In some cases, physiological rationale provides the best guide to patient management. However, EBM suggests that, to the extent possible, clinicians should base their management decisions on findings from systematic reviews of randomized trials. When appropriate, these systematic reviews summarize their findings in meta-analyses that provide single best estimates of the magnitude of treatment impact on patient outcomes.

The history of systematic reviews of thrombolytic therapy provides evidence in support of EBM. Figures 1 and 2, from a paper by Antman and colleagues, depict cumulative meta-analyses of the evidence concerning the impact of thrombolytic therapy and prophylactic lidocaine on death rates in patients suffering from myocardial infarction.[3] The horizontal line in the centre of the left portion of Figure 1 represents an odds ratio of 1.0. An odds ratio of 1.0 denotes that thrombolytic therapy neither increases nor decreases the likelihood of dying. Values to the left of the line indicate that treatment is beneficial and reduces death rates; values to the right suggest that treatment is harmful and increases death rates.

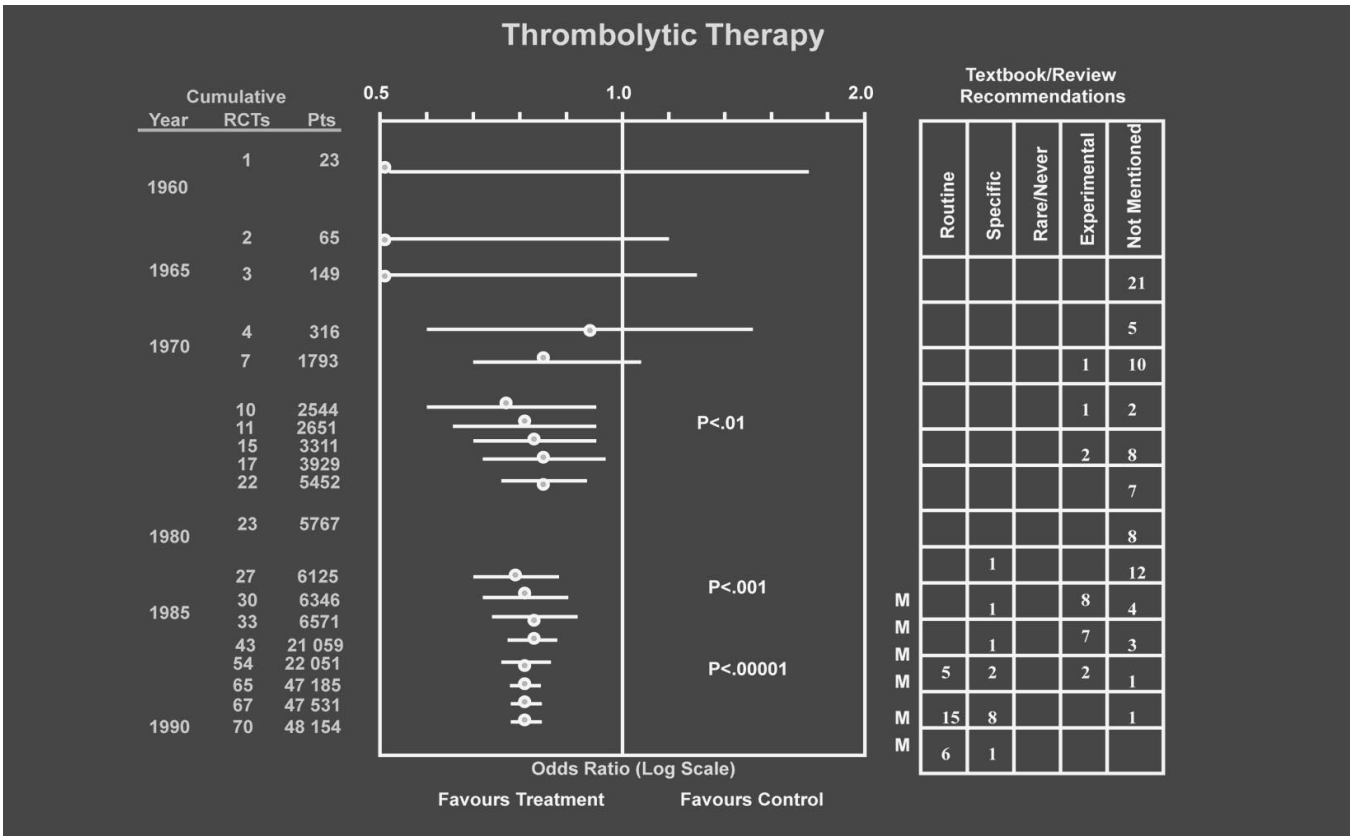

Figure 1. The effect of thrombolytic therapy in preventing death from myocardial infarction. The cumulative meta-analysis by year of publication of randomized control trials (RCTs) are presented on the left. The cumulative number of trials and patients (Pts) are also presented. On the right, the recommendations of the clinical expert reviewers are presented in 2-year segments; except for the entry in 1966, which represents all previous years. The letter M indicates that at least one meta-analysis was published that year. See text for explanations.

Reprinted by permission of *JAMA*. From Antman EM, Lau J, Kupelnick B, *et al.* (1992) "A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction." *JAMA*. 268: 240-248.

The first randomized trial of thrombolytic therapy in the late 1950's, designated "1" in figure 1, enrolled 23 patients. Results suggested that thrombolytic therapy could result in a 50% reduction in the odds of dying. However, the 95% confidence interval around that point estimate suggests that the results were also consistent with an odds of dying with thrombolytic therapy of almost 2.

After investigators completed the second trial of thrombolytic therapy (designated "2") a total of 65 patients had participated in trials – 23 in the first trial, 42 in the second. The point estimate continued to suggest a 50% odds reduction. The confidence interval, while narrower, was still wide. As the data continued to accumulate, the point estimate suggested smaller odds reductions, closer to 25%, and the confidence interval began to narrow. By the early 1970s, when over 2,500 patients had been enrolled in 10 RCTs, the confidence interval no longer crossed 1.0, suggesting a real effect of thrombolytic therapy on decreasing death rates. In the 1980s, when over 6,000 patients had been enrolled in 27 trials, the confidence interval indicated that odds reductions of less than 10% were very unlikely.

Did these data mean an end to RCTs of thrombolytic therapy? No, it did not. After the "answer" (that thrombolytic therapy is beneficial to patients who have an MI) was in, another 40,000 patients were enrolled in trials of thrombolytic therapy. Half these patients received placebo or standard care; they were denied the benefits of thrombolytic therapy, and some therefore died unnecessarily. By 1990, when over 48,000 patients had been enrolled in 70 RCTs, the confidence interval around the odds ratio was extraordinarily narrow.

Why was it necessary to enrol an additional 40,000 patients in RCTs after the benefits of thrombolytic therapy became evident? The right side of Figure 1 provides at least part of the explanation. This part of the figure categorizes experts' recommendations published in textbooks and journal articles as these data were accumulating. In the latter 1980s, recommendations varied between experts. These

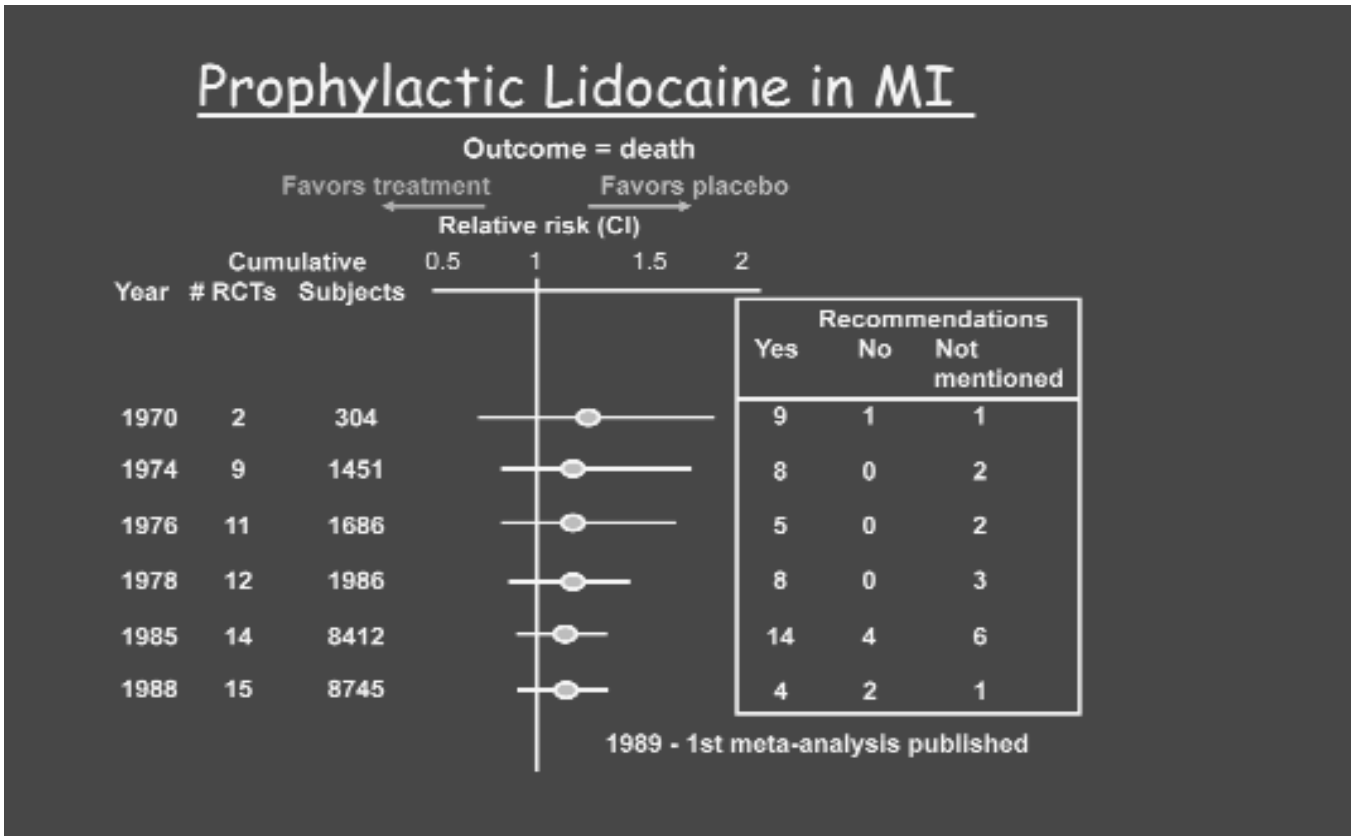

Figure 2. Cumulative meta-analysis of the effect of prophylactic lidocaine in preventing death from myocardial infarction. As in the previous example, this figure shows the expert opinion differs from available evidence and that expert opinion varies.

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ranged from suggestions that thrombolysis be administered routinely to all myocardial infarction patients, to categorizations of thrombolysis as an experimental therapy, to not even mentioning thrombolysis. The right side of Figure 1 suggests two conclusions. First, experts often disagree, offering contradictory recommendations. Second, recommendations may lag substantially behind the data. It was almost a decade after the benefits of thrombolysis became evident that experts consistently recommended thrombolytic therapy for patients with myocardial infarction.

Figure 2 depicts the history of routine administration of prophylactic lidocaine to patients with myocardial infarction. In this case, there was never any RCT evidence supporting prophylactic lidocaine therapy. Did this stop the experts from recommending routine lidocaine administration? No, it did not. Indeed, up until 1989 when the first meta-analysis was published, the majority of experts continued to recommend prophylaxis as standard therapy for myocardial infarction patients. There was, however, the same sort of substantial variability in expert recommendations throughout the 1980s as we observed with thrombolysis. Evidence-based recommendations were not available at the time these data were accumulating because the fundamental methodology used to develop such recommendations, the systematic review, had not been applied to the data in question.

Had evidence-based recommendations been available, from the early 1980s they would have consistently recommended thrombolysis. Following the second key criterion for evidence-based recommendations, that values and preferences underlying the recommendations be made explicit, they would have been qualified with statements that the recommendations placed a relatively high value on preventing premature death, a readiness to incur additional health care costs to achieve that objective, and that patients who were extremely stroke averse might decline thrombolysis. On the other hand, throughout the 1980s, evidence-based recommendations would have consistently recommended against prophylactic lidocaine. Initially, the recommendations would have been qualified with the proviso that risk-taking patients might wish to receive the treatment. As the data accumulated, however, the recommendation against lidocaine would have become progressively stronger.

It is not difficult to offer other such examples of discrepancies between recommendations arrived at through traditional approaches to medical decision-making, and those developed using evidence-based approaches. Consider hormone-replacement therapy (HRT). For over a decade, recommendations from a wide variety of august bodies strongly favoured the widespread use of HRT. These guidelines failed to acknowledge the weakness of the evidence from traditional observational studies, which suggested that HRT decreased cardiovascular risk. This resulted in recommendations that favoured the long-term use of HRT. The subsequent publication of two randomized trials suggesting that HRT does not decrease, and may increase, cardiovascular risk, has reversed recommendation.[4,5] Such examples highlight the limitation of traditional approaches when making health care decisions. They provide the evidence that evidence-based approaches often yield courses of action more in accord with patients' long-term best interests.

THE EVOLUTION OF EVIDENCE-BASED MEDICINE

In 1992, an article that one might describe as an EBM manifesto appeared in the *Journal of the American Medical Association (JAMA)*.[6] The article emphasized four important differences between EBM and traditional medical practice. The authors suggested that: 1) EBM places a higher value on systematically collected evidence and a lower value on unsystematic clinical observation; 2) EBM places a higher value on experiments that focus on outcomes that are important to patients, and a lower value on physiological rationale; 3) that interpreting the medical literature was a key skill for clinicians, and that a formal study of rules of evidence was necessary for a skilled interpretation; 4) finally, that EBM places a higher value on the independent assessment of the individual clinician and a lower value on authority.

Less than a decade later, the 25th and final instalment of the *JAMA* series of Users' Guides to the Medical Literature took a somewhat different approach in describing the principles of EBM.[7] This article described two key elements of the EBM approach. The first was a hierarchy of evidence going from the strongest (N of 1 randomized trials, followed by systematic reviews of randomized trials) to the weakest (physiological rationale and unsystematic clinical observation). The second key element suggested that evidence, itself, was insufficient for making health care decisions, and that values and preferences must be part of every decision.

Another major step in the evolution of thinking about EBM made the distinction between evidence-based *practitioners* and evidence *users*.[8] Most EBM *practitioners*, the authors argued, will understand the fundamental principles of differentiating strong from weak evidence, and will be able to understand estimates of the magnitude of risks and benefits of the management strategies they are considering. They will be able to identify evidence-based synopses and summaries of the literature, and evidence-based guidelines and recommendations that follow from the evidence, and will rely on these sources to guide their practice. In contrast, evidence *users* comprise a minority of clinicians with a high level of expertise in interpreting the original medical literature.

A mature presentation of the principles of EBM emphasizes how EBM fits into a humanistic approach to the practice of medicine that fully acknowledges the clinicians' responsibility to the community, the need for a compassionate and empathetic practice, and the primacy of patient and societal values and preferences in medical decisions.[9] This discussion in the Users' Guides puts great emphasis on the limitations of evidence in making medical decisions, and the need for incorporating values and preferences. Key passages include the following description of the first principle of EBM, that evidence alone is never sufficient to establish the best course of action:

> *"Picture a patient with chronic pain resulting from terminal cancer. She has come to terms with her condition, has resolved her affairs and said her goodbyes, and she wishes to receive only palliative therapy. The patient develops pneumococcal pneumonia. Now, evidence that antibiotic therapy reduces morbidity and mortality from pneumococcal pneumonia is strong. Almost all clinicians would agree, however, even evidence this convincing does not dictate that this particular patient should receive antibiotics. Despite the fact that antibiotics might reduce symptoms and prolong the patient's life, her values are such that she would prefer a rapid and natural death.*
>
> *Now envision a second patient – an 85-year-old man with severe dementia, who is incontinent, contracted, and mute, without family or friends, who spends his days in apparent discomfort. This man develops pneumococcal pneumonia. Although many clinicians would argue that those responsible for this patient's care should not administer antibiotic therapy because of his circumstances, others, by contrast, would suggest that they should do so. Again, evidence of treatment effectiveness does not automatically imply that treatment should be administered. The management decision requires a judgment about the trade-off between risks and benefits; and because values or preferences differ, the best course of action will vary from patient to patient and among clinicians.*
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> *By values and preferences, we mean the underlying processes we bring to bear in weighing what our patients and our society will gain – or lose – when we make a management decision. The explicit enumeration and balancing of benefits and risks that is central*

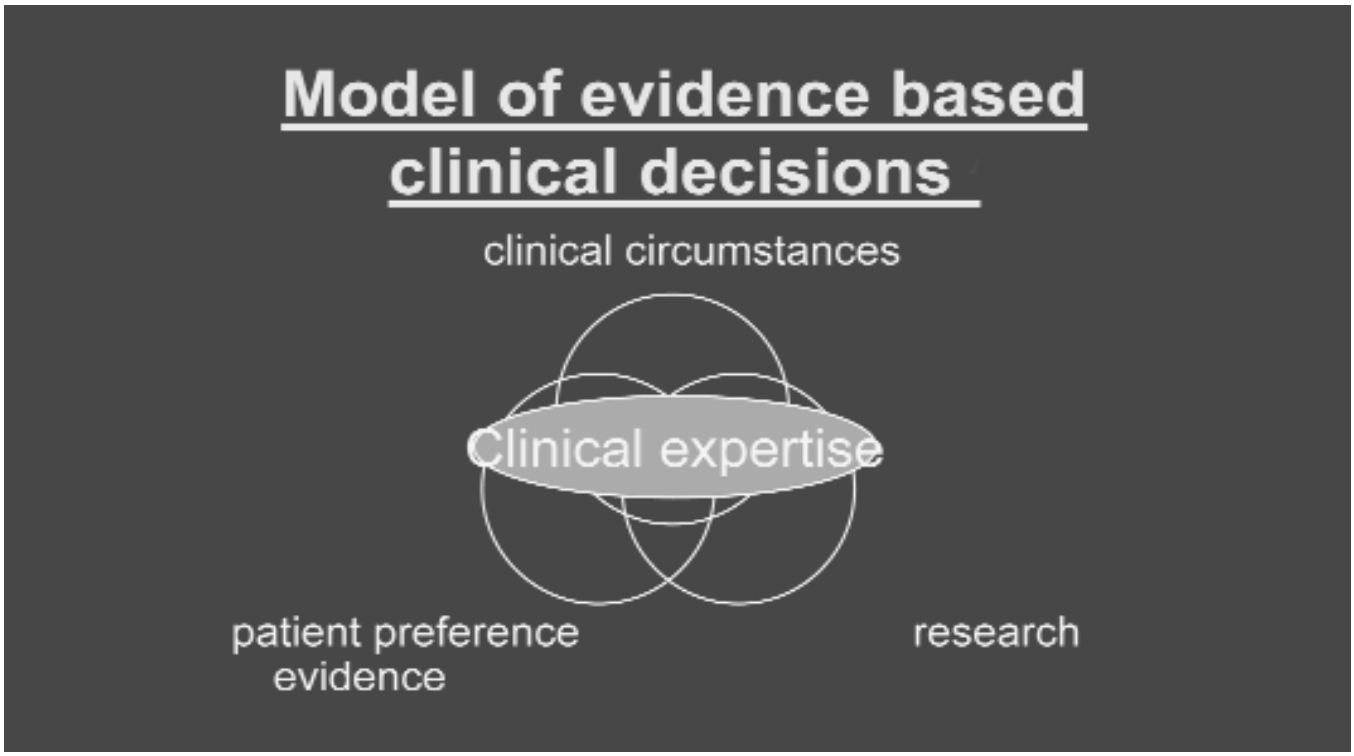

Figure 3. Model of evidence-based practice illustrating the essential components of evidence-based clinical decision making.

Reprinted by permission of the *British Medical Journal*. From Haynes RB, Devereaux PJ, Guyatt GH. (2002) "Physicians' and patients' choices in evidence based practice: Evidence does not make decisions, people do" (Editorial). *British Medical Journal*. 324: 1350.

to EBM brings the underlying value judgments involved in making management decisions into bold relief."

The acknowledgement of the primacy of values and preferences has profound implications for the role of the clinician in the decision-making process. The discussion in the Users' Guides book puts it this way:

"Thus, knowing the tools of evidence-based practice is necessary but not sufficient for delivering the highest quality patient care. In addition to clinical expertise, the clinician requires compassion, sensitive listening skills, and broad perspectives from the humanities and social sciences. These attributes allow understanding of patients' illnesses in the context of their experience, personalities, and cultures. The sensitive understanding of the patient is linked to evidence-based practice in a number of ways. For some patients, incorporation of patient values for major decisions will mean a full enumeration of the possible benefits, risks, and inconvenience associated with alternative management strategies that are relevant to the particular patient. For some of these patients and problems, this discussion should involve the patients' family. For other problems – the discussion of screening with prostate-specific antigen with older male patients, for instance – attempts to involve other family members might violate strong cultural norms.

Many patients are uncomfortable with an explicit discussion of benefits and risks, and they object to having what they perceive as excessive responsibility for decision-making being placed on their shoulders. In such patients, who would tell us they want the physician to make the decision on their behalf, the physician's responsibility is to develop insight to ensure that choices will be consistent with patients' values and preferences. Understanding and implementing the sort of decision-making process patients desire, and effectively communicating the information they need requires skills in understanding the patient's narrative and the person behind that narrative."

This mature understanding of EBM places the patient, in one way, at the centre of the decision-making process. After all, only patients have a full and deep understanding of their circumstances, and their values and preferences. In another way, however, it places the physician at the centre of the process.[10] In most instances, the clinician will be the only party with a full understanding of the direct evidence that bears on the decision. Even with the exceptional patient who

may have read and understood the relevant literature, the clinician will have an understanding of the medical context of the disease process not available to the patient. The clinician, moreover, must judge the manner in which the patient wants to be involved in the decision-making process. Finally, the clinician brings an objectivity that may be crucial in achieving a satisfactory decision-making process, and that is often unavailable to the patient.

These considerations give rise to the model of evidence-based practice presented in Figure 3. The patients' circumstances define the problem. The clinician must make the diagnosis, and must have knowledge of all reasonable management options that might follow from that diagnosis. The clinician must be aware of all the direct and indirect evidence that bears on the relative benefits, risks, inconvenience, and costs associated with the alternative management strategies. The clinician must also ascertain the patient's desired style of decision-making, and how the patient's particular circumstances, and values and preferences, bear on the benefits and down sides of the alternative management strategies.

Ultimately, for one patient, the clinician may present the benefits and down sides of alternative course of actions to the patient, who will make the decision. For another patient, the clinician may present the benefits and down sides, but also offer advice and direction regarding the optimal choice. For a third patient, following a discussion of preferences and values, the clinician might recommend a specific course of action that she believes is in the patient's best interests.

THE FUTURE OF EVIDENCE-BASED MEDICINE

Acknowledging the primacy of values and preferences, patients' differing wishes about their role in the decision-making process, and the respective roles of the clinician and patient, highlights the tremendous gaps in our knowledge about how best to incorporate evidence in the decision-making process. Reaching a full understanding of benefits and down sides of the alternative courses of action is challenging for the expert, to say nothing of the front-line clinician. Our knowledge of how best to ascertain the patients' desired style of decision-making and (to the extent the patient wishes) communicate the magnitude of the benefits and risks remains superficial. The more one considers both the complexity of the process, and the limited time available in the clinical encounter, the greater the temptation to throw up ones' hands in despair at the apparent impossibility of a satisfactory solution.

Nevertheless, as clinicians wanting to do the best for our patients, we cannot retreat from the challenge. As individuals, we make dozens, if not hundreds, of management decisions each day. Most are trivial, a minority are momentous for our patients. Key research and conceptual questions for evidence-based decision makers include the following: how should we decide which decisions warrant using the traditional short-circuit approach, and which merit additional time and energy? How can we best tailor our decision-making style to the patients' wishes? How do we best communicate risk and benefit information to our patients? How do we decide when the outcome of the decision-making process is optimal, and when it is not?

Some may find it ironic that the focus on rigour in making causal inferences and the critical use of the medical literature in clinical practice has led us to a detailed consideration of how to bring patient values and preferences to bear on individual decisions. Personally, I find it fascinating, and exciting. EBM will continue to evolve, possibly to further unexpected destinations.

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Dr. Gordon Guyatt, MD, MSc, is a Professor of Clinical Epidemiology and Biostatistics and Medicine at McMaster University.

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