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Epistemologic Inquiries in Evidence-Based Medicine

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Background: *Since the term "evidence-based medicine" (EBM) first appeared in the scientific literature in 1991, the concept has had considerable influence in many parts of the world. Most professional societies, the public, and funding agencies have accepted EBM with remarkable enthusiasm. The concept of evidence-based practice is now applied in management, education, criminology, and social work. Yet, EBM has attracted controversy: its critics allege that EBM uses a narrow concept of evidence and a naive conception of the relationships between evidence, theory, and practice. They also contend that EBM presents itself as a radical restructuring of medical knowledge that discredits more traditional ways of knowing in medicine, largely in the interests of people with a particular investment in the enterprise of large-scale clinical trials. Because EBM proposes a specific relationship between theory, evidence, and knowledge, its theoretical basis can be understood as an epistemological system. Undertaking epistemological inquiry is important because the adoption of a particular epistemological view defines how science is conducted.*

Methods: *In this paper, we challenge this critical view of EBM by examining how EBM fits into broad epistemological debates within the philosophy of science. We consider how EBM relates to some classical debates regarding the nature of science and knowledge. We investigate EBM from the perspective of major epistemological theories (logical-positivism/inductivism, deductivism/falsificationism/theory-ladeness of observations, explanationism/holism, instrumentalism, underdetermination theory by evidence).*

Results: *We first explore the relationship between evidence and knowledge and discuss philosophical support for the main way that evidence is used in medicine: (1) in the philosophical tradition that "rational thinkers respect their evidence," we show that EBM refers to making medical decisions that are consistent with evidence, (2) as a reliable sign, symptom, or mark to enhance reasonableness or truthfulness of some particular claim ("evidence as a guide to truth"), and (3) to serve as a neutral arbiter among competing views. Our analysis indicates that EBM does not have a rigorous epistemological stance. In fact, EBM enthusiastically draws on all major traditions of philosophical theories of scientific evidence.*

Conclusions: *Our findings indicate that EBM should not be construed as a new scientific or philosophical theory that changes the nature of medicine or our understanding thereof. Rather, we should consider EBM as a continuously evolving heuristic structure for optimizing clinical practice.*

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Abbreviations used in this paper: EBM = evidence-based medicine, RCT = randomized controlled trial.

See the Glossary at the end of the article for definitions of the italicized terms used in this paper.

Introduction

Although the term *evidence-based medicine* (EBM) first appeared in the scientific literature in 1991,[1] it was a 1992 article in *JAMA* that drew the attention of a wider medical audience.[2] While the antecedents of EBM go back at least 50 years or, depending on one's perspective, several hundred years,[3] the clear articulation of EBM as a coherent approach to medical practice marks a turning point in the relationship between medical evidence and practice. In 2001, *The New York Times* judged EBM as the idea of the year with respect to the procurement of *knowledge* in medicine.[4] Recently, health care opinion leaders concluded that EBM represents one of the most important medical milestones of the last 160 years, in the same category as innovations such as antibiotics and anesthesia.[5]

This increasing recognition of EBM and its adoption by professional societies as well as public and funding agencies have provoked epistemological inquiry.[6] *Epistemology* is the philosophical study of the nature of knowledge and the evaluation of claims that something is known or that some particular agent knows something. Do we as a scientific community know that the Earth revolves around the Sun? Do we as individuals know it? In addressing the first question, we are led to ask questions about the justification of scientific theories and the evaluation of the reliability of different sorts of evidence; to answer the second question, we need to understand the nature of beliefs held by individuals and the different ways those individuals can acquire true (and false) beliefs. Naturally, these two inquiries overlap, but they have a rather different emphasis. The former inquiry overlaps to a significant extent with the philosophy of science, which is the branch of philosophy concerned with understanding the nature of scientific theories, how they change, and how they can be tested.

What is the relationship between EBM and various theories of knowledge advanced by philosophers of science in recent years? This question is important because on the face of it, EBM makes important claims about both the theory and practice of medicine. EBM makes a normative claim about when some kinds of medical knowledge can genuinely be taken as knowledge. It also makes a normative claim about medical practice: Wherever possible, the choice of diagnostic test, preventive measure, or treatment should be based on the best available evidence about the available interventions. EBM thus makes medical knowledge central to ethical medical practice in a rather strong way and also uses a stringent criterion for what should count as medical knowledge.

Critics of EBM commonly attack its epistemological credentials in one of two ways: (1) they allege that EBM uses a narrow concept of evidence and a naive conception of the relationships between evidence, theory, and practice, or (2) they allege that EBM is (or presents itself as) a radical restructuring of medical knowledge that discredits more traditional ways of knowing in medicine, largely in the interests of people with a particular investment in the enterprise of large-scale clinical trials.

Our thesis is that much of the criticism of EBM from a theoretical point of view is misplaced in that these criticisms can be leveled at any scientific theory or methodology; they are general questions about the justification of scientific theory rather than specific criticisms of EBM as such. Thus, while they are useful in helping not only to clarify our thoughts about scientific clinical medicine, but also to alert us to the possibilities of misusing concepts or making unjustifiable claims, they are not fatal to the enterprise of EBM as a practical approach to improving the quality of medical care by eliminating dangerous or ineffective treatments, promoting the use of well-tested treatments, and stimulating the evaluation of treatments where there is reasonable uncertainty about their merits.

Because EBM proposes a specific relationship between theory, evidence, and knowledge, the theoretical basis of EBM can be understood as an epistemological system. Thus, EBM can be examined by considering how it relates to several of the classical debates in epistemology. We do not discuss these issues in detail but rather show how debates about EBM reproduce standard debates in the philosophy of science in general. We believe that undertaking this exercise will be useful to both philosophers of science (who may better appreciate complexities of medicine in general and EBM in particular) and practicing physicians (who may come to understand intimate relevance of many philosophical concepts to science and practice of medicine). We hope that both parties will acknowledge that there is no epistemological "one size fits all" approach that applies to the entire practice of EBM and that narrow focus on EBM (such as a mistaken view that EBM accepts findings from randomized controlled trials [RCTs] as the only admissible evidence for practice of medicine[7-11]) can be dispelled by our debate of EBM from the point of philosophy of science.

We have organized our paper in six separate but related sections. In the first section, we discuss the relationship between observable phenomena and unobserved or unobservable features of reality. In the second, we examine EBM from the point of view of the importance of getting our observations correct, ie, the importance of the reliability of observations and measurements. The third section addresses the testing of scientific hypotheses. We present EBM from the point of view of three major epistemological views of evidence: *inductivism*, *falsificationism*, and *explanationism*. This third section also addresses related concepts: theory-ladenness of observation and the underdetermination of theory by data. Fourth, we discuss the nature of "scientific methods" and sociohistorical views of scientific evidence, and we propose that EBM has emerged as a reaction toward increasing dissatisfaction with the practice of medicine. Fifth, we debate EBM from the point of view of authority of scientific knowledge in resolving practical disputes. We frame the issue by asking if EBM is a democratic force, "liberating" patients and the public, or an authoritarian one that must be practiced within rigidly defined rules and principles. In the sixth section, we summarize our walk through the history of epistemological concepts by stressing the central role of evidence.

We conclude by highlighting key criticisms of EBM and by providing our own thoughts how EBM will evolve in the future.

These are central themes in understanding the relationship between theory, evidence, and knowledge.

Since these concepts often overlap, their separation may artificially blur the importance of the issues we hope to cover in the next six sections.

A simplified narrative of an epistemologist's view regarding medical research is described in the box below.

We limit ourselves to *empiricism* and do not consider *rationalism*, which insists that reason alone rather than empirical observation can be a source of knowledge.[12]

Evidence and Knowledge

Before we embark on our main thesis, we first want to highlight the difficulties in defining the concept of evidence and disagreements about the nature and definition of evidence that have been debated by most prominent philosophical minds.[13] For a start, different languages translate "evidence" in different ways; some consider it synonymous with "proof," "fact," or "knowledge." Philosophers theorize evidence in different ways, too. For example, two great empiricists of the 20th century, Bertrand Russell and Willard Van Orman Quine, had different interpretations of evidence. Russell thought of evidence as sense data, ie, mental items of one's present consciousness that are immediately familiar to the observer. Quine defined observational sentences as the vehicle of scientific evidence; these are sentences that are "directly and firmly associated with our stimulations" and on which speakers of the language can agree outright on witnessing the occasion[13,14] (ie, "It is getting cold," "It's raining," etc). Other philosophers have defined evidence differently.[13] The least controversial definition of evidence is that it represents "grounds for belief," "that which justifies belief."[12,13] Philosophers have even more strongly disagreed about the definition and nature of knowledge.[12,15,16] However, virtually all agree that "true belief" is a necessary condition for knowledge.[12] The debate continues whether this true belief needs to be justified, causally explained, or only acquired by a reliable process or method.[12]

Although not universally agreed upon,[13] there is a crucial difference between evidence and knowledge. The evidentiary basis for belief may not be necessarily true, while "true" belief is a prerequisite for the definition of knowledge. However, as explained later, what counts as "true" scientific knowledge is tentative and remains revisable as science progresses. EBM accepts a notion of gradation of evidence,[17] implying that particular claims can be confirmed by given evidence to various degrees and that evidence can be misleading.[13] The emphasis of EBM on skepticism and uncertainty — we will never be sure of the magnitude of the effects of our treatments or the power of our diagnostic tests — is central to the approach and agrees with the philosophical view that scientific knowledge is never complete and ultimately fallible (see below).

These are difficult epistemological concepts that continue to be debated by professional philosophers within various schools of thoughts on the nature and interpretation evidence (ie, foundationalism, evidentialism, coherentism, reliabilism, etc).[18] The details of these arguments are beyond the scope of this paper.

In the context of EBM, evidence is being used at least in three different ways, each of which has its philosophical support.[13]

(1) *"Rational thinkers respect their evidence."* Eddy,[19] for example, defines EBM as "a set of principles and methods to ensure that, to the greatest extent possible, population-based policies and individual decisions are consistent with evidence of effectiveness and benefits." "To be called 'evidence-based,' the decision must at least be consistent with whatever evidence does exist."

(2) *Evidence as a guide to truth*. In the context of EBM, evidence is often used as a reliable sign, symptom, or mark of that which it is evidence of, ie, evidence "points beyond itself" to enhance reasonableness or truthfulness of some particular claim[13] — for example, as when "positive" diagnostic test increases the likelihood that our patient truly has a certain disease. This is

An Epistemologist's Simplified View of Medical Research:

If we want to test a hypothesis in medicine — for example, that aspirin is effective in alleviating headache pain — we must carry out a series of observations but inevitably will conduct only a finite number of observations to test a hypothesis that is supposed to be universally valid. Thus, we go beyond the observations we are able to collect, and we are testing a claim about a feature of reality we cannot observe directly (in part, the claim that aspirin affects particular physiological mechanism that causes the subjective feeling of pain involved in a headache). We may be concerned with how best to conduct the series of observations as to avoid bias and missing deviant cases; therefore, we are concerned with the reliability of our observations. Most scientists (and most people generally) are aware of the psychological tricks that can lead us to see what we wish to see or miss things we do not expect to see (which more generally is the issue of the theory-ladenness of observation). A further implication of the way we use finite sets of data to test theories is that any given set of data can support (infinitely) many different theories (so we may tend to fit straight lines to sets of data, but there is no theoretical reason why we cannot fit polynomial curves, for instance). Overarching these issues is a more general question of whether there is a single scientific method (or even just a small family of scientific methods) that provides a "royal road to truth." Conversely, does the fact that a claim has been tested using such methods guarantee that it is more robust and reliable than beliefs acquired in other ways and therefore should be treated as more authoritative than other beliefs in determining what to do? This last issue has a political flavor, too, in that it is easy to move from holding that scientifically tested beliefs are more authoritative to holding that scientists themselves should have more authority than non-scientists when it comes to assessing knowledge, claims or practical proposals.

also typical way how evidence is employed in scientific testing: to support or disconfirm a given hypothesis. [In this view, evidence is not synonymous with facts. If one identifies evidence with factual knowledge, then any inconsistency with evidence automatically means inconsistency with some truth. This is not the case when evidence is taken as " grounds for belief." Inconsistency with one's beliefs does not mean that findings or propositions are necessarily false.[13]]

(3) *Evidence as a neutral arbiter among competing views*. This is probably the original reason for the introduction of the EBM movement: there is well-documented variation in the practice of medicine, the chief source of which is the lack of reliable evidence.[20] If high-quality evidence can be generated and disseminated to practicing physicians, one would hope that it can serve as a powerful vehicle to help reconcile different views on the practice of medicine. This, in turn, would result in less variation in the practice of medicine.

Below we explore in details various epistemological views relating to a different role of evidence in the context of clinical research. The analysis can explain why (similarly to the situation in philosophy), "the concept of evidence has been called upon to fill a number of distinct roles."[13] As a result, and depending on one's view, EBM has been widely (mis)interpreted in both professional and lay literature.

A Relationship Between Observed Vs Observable Vs Unobservable Reality

The 1992 *JAMA* paper challenged the preeminence of physiological (causal-inductive reasoning) in medicine.[2] "Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making, and stresses the examination of evidence from clinical research… Evidence-based medicine requires new skills of the physician… and the application of formal rules of evidence in evaluating the clinical literature."[2] These statements presage a continued campaign that has, to some extent, succeeded in shifting the scientific discourse from theory and causal-inductive reasoning to the reliable, rigorous, and critically scrutinized empirical observations in real-life clinical situations.

EBM researchers and educators have developed rules of evidence,[21,22] as epitomized by various schemes of hierarchy of evidence,[23] to help users organize these empirical findings across a gradient of credibility or reliability. In this view, the degree of belief we place in inference should be directly related to the underlying quality of the evidence.[24-26] The premise is an assumed link between high-quality evidence and "truth."[13,27] The role of evidence is to serve as a reliable indicator helping to make something evident that would not be so in its absence.[13]

The concept that reliable empirical observation (ie, fundamental units of evidential significance), together with rules of evidence that separate "truth" from "falsehood" (in clinical research), is reminiscent of *logical-positivism* — a movement that dominated the philosophy of science about 80 to 90 years ago. Like logical-positivism in the early 20th century, EBM today has re-exposed a central tension in epistemology regarding the relationship between observed reality and unobservable reality.

In other words, how far can we go beyond our observations and arrive at some valid inferences?[27-29] This recurring tension in science and epistemology — on one hand, we must limit ourselves to experience, while on the other hand, we must go beyond experience — has been in existence since the time of David Hume, a great 18th-century empiricist philosopher. The positivist approach to theory is that we can make true assertions only about directly observable entities and that only meaningful statements are those that are capable of being true or false.[30] Theories should be considered as instruments that serve as a link between observational inputs (observed reality) and observational outputs (yet unobserved but observable reality [this view is known as *instrumentalism*]). Theories do not attempt to accurately describe unobservable reality but rather to predict empirical findings. Both EBM and logical-positivism suggest that the role of theories is not to accurately describe the world but to accurately predict empirical observations.[27,30] Theories do not need to be true to serve as useful links between observed reality and observable (but not observed) as well as unobservable reality. For example, the drug erythropoietin is shown to improve fatigue in cancer patients (observed through patient reports that they feel better).[31] From these observations, we can predict that future patients (who are yet to be observed) will also feel better after administration of this drug. We can speculate about the underlying mechanism of the drug (ie, whether it produces its effects by increasing the level of hemoglobin or binding to hypothetical erythropoietin "fatigue" receptors) and its effects on patients (subjective feelings of fatigue), but direct evidence of the true effect of erythropoietin will remain unobservable. Like positivism, EBM suggests we should restrict ourselves to the observed reality, and when we go beyond our observations, the focus is on extending our inferences about the unobserved world. Reality, however, remains ultimately unknowable.[28,29] This positivist approach has some affinities with EBM, which for instance tends to privilege knowledge about what can be shown to work over deeper questions about why it does so. However, the logical-positivist stance is too restrictive. Logical-positivists consider any statements that are not true by definition (analytic) or that correspond to empirical findings (synthetic statements) as nonsense.[32] In other words, anything that is in principle observable but not observable at a given time

would be classified by logical-positivists as nonsense.[32] EBM, on the other hand, often proceeds as in the example of the collation of studies in meta-analysis to allow convergence on the underlying truth that is only indirectly observable. For example, individual trials were inconclusive as to whether a blockade of estrogen receptors by the drug tamoxifen helps reduce the risk of recurrence of breast cancer. However, when a meta-analysis of all these trials was performed,[33] the practice of treating breast cancer had changed dramatically; all oncologists (and their patients) accepted the "truthfulness" of the claim that tamoxifen decreases recurrence of breast cancer by blocking estrogen receptor, a claim that was only indirectly observable. Hence, EBM need not be taken as positivist science, and advocates of EBM are not committed to positivist theses about meaning and truth in science and medicine or about the kind of facts that can be known or not known.

Getting Our Observations Correct

In one way, EBM can be construed as a reaction to the fallibility of our observations. Research over the last several decades has convincingly pointed out that medical research is subject to biases with the consequence that many clinical research findings ultimately prove false.[34-36] Promotions of treatment based on unreliable research findings such as prescribing estrogen hormone replacement to healthy women on the basis of a hypothesized reduction in cardiovascular risk have misled many patients.[37] Some putatively beneficial treatments, including bone marrow transplant for breast cancer[38] and the use of prophylactic antiarrhythmics in patients with myocardial infarction,[39] have resulted in thousands of avoidable deaths. For example, the use of prophylactic antiarrhythmic agents resulted in more deaths than the Vietnam war caused.[40]

Of prime concern, therefore, is the development and promotion of a universal set of scientific rules that ensure accurate inferences on the basis of experience.[27,28] The aim of pathophysiological knowledge in understanding the mechanism of diseases is useful insofar as it helps frame hypotheses and predicts the results of experiments such as those conducted in RCTs. For example, pathophysiological studies showed that the use of prophylactic antiarrhythmic agents in patients with myocardial infarction reduced arrhythmias. From this, it was deduced that giving prophylactic antiarrhythmic to these patients will result in improved survival. Only when these hypotheses were subjected to rigorous experimental testing in RCTs did it become evident that these pathophysiologically based theories were disastrously flawed.[41] Although EBM stresses the importance of reliable observations over theory, this stance is not rigid. As we will discuss later in the example of homeopathy, the lack of credible theory trumped seemingly rigorously obtained observations.

The emphasis of EBM on a meticulous method with clearly operationally defined concepts and procedures is reminiscent of another epistemological view, that of *operationalism,* originally popularized by physicist Percy W. Bridgman in the 1920s.[30,32] Operationalism requires that all scientific terms are defined as constructions from measurable entities. "If we don't know how to measure something, we don't know what we mean by it."[27,30,42] As a result, EBM innovators have produced numerous standardized statements and checklists to help interpret or conduct research.[43-45] Yet, EBM does not follow operationalism in all relevant respects. While EBM and operationalism may appear similar in how they conceptualize scientific knowledge, they evaluate the validity of scientific claims differently. Bridgman identified the scientific concept as a synonym with the corresponding set of operations.[32] However, the operationalism of EBM is merely heuristic in providing practical rules for doctors and others in assessing how to treat and diagnose disease in the face of practical uncertainty. The operationalism approach is often too restrictive in clinical medicine since many concepts (eg, patients' well-being or preferences) defy easy measurements and translation into variables consisting of specific observations. Qualitative research often provides insights that may not be captured through a restrictive operationalistic approach, but this is merely a different kind of empirical evidence that provides no better access to underlying reality than quantitative data. On the other hand, qualitative research can and does challenge the operationalist's implicit claim that what cannot be measured quantitatively is unobservable or at least "merely" subjective.

EBM's operationalism is a thesis not about the fundamental epistemology of scientific claims in medical theory, but rather concerning practical rules about appraising scientific claims and improvement in medical practice.

Does EBM Offer a New Theory of Medical Evidence?

The previous section placed EBM in a broad philosophical context. The question remains whether EBM posits a unique view on the generation of evidence and its use in scientific reasoning. We believe not. Indeed, EBM has embraced most of the forms of scientific reasoning that have been developed so far. Broadly speaking, there are three major theories of scientific reasoning: *inductivism*, *falsificationism,* and *explanationism (holism)*.[29,30]

Inductivism

The first widely adopted empirical theory is the causal-inductive view of scientific evidence, originally introduced by Isaac Newton and later further developed by John Stuart Mill.[29] The most popular form consists of inductive generalization, which involves reasoning

from a limited number of observations to wider, more probable generalizations. Inductive reasoning is the dominant reasoning form in science and medicine and may be employed in simple forms or via the Bayesian probability calculus.[29,30] Examples of inductive reasoning include inferring diagnosis from a set of symptoms, reasoning through analogies, or generalizing the results from clinical trials to be used in practice guidelines.[46-48] The major problem with inductive use of scientific evidence is that no matter how many individual observations were correctly observed in the past, there is no logical guarantee that the next unobserved event will resemble the previous observed ones.

Falsificationism

The second view of scientific evidence is known as *falsificationism*, which was developed as a reaction toward the problem of induction and the failure of logical-positivism to develop a verification principle.[49,50] According to the verification principle, a statement is meaningful if it either states a logical *tautology* or is in principle capable of empirical verifiability. A statement is verifiable if it can be supported by direct observation or if we can use it to derive statements that are themselves directly verifiable and cannot be derived without it.[51] A crucial difficulty here, according to Popper,[49] is that a scientific hypothesis can never be proven; it can only be falsified or rejected. A good scientist tries to disprove a hypothesis. If after a rigorous testing the hypothesis is not refuted, it remains corroborated (but never proven). Although scientific method is the best we have to understand the world around us, scientific knowledge is never complete; it will always be revisable and ultimately fallible.[52] This view is known as *fallibilism*. Only falsifiable theories are good theories. This view rejects inductivism and maintains that *deductivism* embodies the standards of scientific reasoning.

Modern clinical research has widely embraced hypothesis testing and falsificationism. In fact, all clinical trials based on the frequentist (ie, non-Bayesian) approach rely on the reasoning in which the null hypothesis (of, say, no difference between two treatments) is rejected.[53] It should be mentioned that in the strict Popperian sense, rejection of the null hypothesis should not be equated with acceptance of the alternative hypothesis. However, as a rule, clinicians and investigators are not scrupulous in avoiding this additional inference: Rejection of the null hypothesis is usually automatically equated with acceptance of the alternative hypothesis.[47,48,53]

EBM endorses scientific inquiry based on a solid rationale for undertaking an investigation and, in this sense, acknowledges the importance of an a priori hypothesis underlying the conduct of clinical research. However, EBM rejects conventional hypothesis-testing — meaning the binary yes/no, works/doesn't work approach associated with the threshold *P* value of .05 — as misleading. Rather, EBM encourages an estimation approach: trying to determine the most likely effect, and the range within which the effect plausibly lies (typically as represented by the 95% confidence intervals).[54]

Popper[49] and a score of other philosophers,[55,56] also maintained that our observations are *theory-laden,* ie, observations cannot be independent of theories within which they were made. EBM does not appear to have a consistent view on the issue of whether evidence can be neutral, ie, interpretation can be divorced from a particular theoretical construct. We saw earlier that, by and large, observations obtained in the clinical trial on hormone replacement therapy were accepted as accurate despite contradicting the prevailing theory of the day (resulting in the change of practice almost overnight). However, results from homeopathy trials that were obtained from RCTs were dismissed to a large extent due to the extreme skepticism regarding homeopathic theory.[57] Evidence obtained in homeopathy RCTs consists of high-quality placebo-controlled trials in that both patients and physicians were "blinded" to intervention.[57] However, homeopathic drugs are prepared by serial dilutions of remedy, the result of which is that the drug is diluted to the point that there is little to no likelihood that a single molecule from the original solution is present in the final product. As a result, the homeopathic solution is not believed to adhere to contemporary chemical principles, thereby making any claim about its effects pharmacologically implausible.

Scientific testing is a complex endeavor, and a straightforward falsification pointing to one set of explanations is rarely achieved. Is one treatment truly better than the other? Or might one approach appear to be superior because randomization failed to balance the prognostic characteristics, or because our observations were not "blinded," or because an excessive number of patients were lost to follow-up? Each of these assumptions (auxiliary hypotheses) is in principle falsifiable, but in many cases not practically so. This led Quine to argue that science is *underdetermined,* ie, evidence is always compatible with more than one explanation and there is no logical basis to conclusively derive the truthfulness or falseness of any statement.[14,30]

Holism

Scientific testing should take into account our entire "web of beliefs."[14] This is the third view of scientific evidence known as *holism,* originally developed by William Whewell[29] and then by Quine. The view is also known as *abduction*[32] or *inference to best explanation* or *explanationism*.[29] In this framework, the hypothesis is confirmed by coherence in the explanation and prediction of observational phenomena across disciplines[58,59]; this is often termed as *consilience*.[60] Thus,

any new scientific evidence should be integrated in and contrasted with the totality of our beliefs and knowledge.[14,28,58] EBM has strongly embraced the idea that medical practice should be based on the totality of evidence.[61] This is best epitomized by the birth of the Cochrane Collaboration, an international organization devoted to the development, preparation, maintenance, and dissemination of systematic reviews (ie, synthesis of the totality of high-quality evidence) regarding the effects of health care interventions.[62]

Although for practical purposes systematic reviews of RCTs are most often performed, the principle of totality of evidence applies to all other forms of evidence. As a result, an increasing number of systematic reviews of observational studies, including diagnostic and prognostic studies, are being conducted. Those performing systematic reviews are encouraged to discuss their findings across all disciplines. The similar view that EBM should be integrated with basic science and nonclinical evidence across the entire web of our scientific beliefs was proposed by Sehon and Stanley.[63]

From these considerations it becomes obvious that EBM does not represent a new or special theory of knowledge. In fact, EBM enthusiastically draws on the major traditions of philosophical theories of scientific evidence. However, EBM does stress the importance of reliable, unbiased observation over theory. The above considerations also highlight the relevance of general epistemological concepts in the way that clinical research is carried out — *adoption of a particular epistemological view defines how science is conducted*. For example, if we adopt the causal-inductive epistemological view and are interested in confirming inductive inferences, then our approach should rely on accumulation of masses of data. The recent technological innovations have reinvigorated the interest in this epistemological view, as witnessed by widespread penetration of this type of scientific approach in health outcome research, genomics, proteonomics, etc. However, if we believe that our observations are theory-laden, we will rely on hypothesis testing using deduction and falsificationism, as exemplified by using RCTs to address a given hypothesis about the effects of competing treatments. On other hand, if we take a stand that both inductive and deductive approaches are inadequate for the practice of science,[32] then we will embrace abduction ("inference to best explanation") as the desired epistemological approach to the practice of science. The Table summarizes these three major epistemological approaches and their relevance to medical research, and it highlights how adoption of a particular epistemological view defines how science is conducted.

Table. — Major Epistemological Theories and Their Relevance to Clinical Research

1. Induction (inductivism) (data-driven approach)
   - Causal-inductive view (physiologic/deterministic vs statistical approaches)
     - — If we are interested in confirming inductive inferences then our approach should rely on accumulation of masses of data
       - – Widespread penetration of information technology has revived interest in this type of scientific approach (health outcome research, genomics, proteonomics etc)
     - — Bayesianism
       - – Most decision-support systems employ Bayesian (inductive) calculus
2. Deduction (falsificationism) (theory-driven approach)
   - Only falsifiable theories are good theories
     - — Modern clinical research (eg, RCTs) has widely embraced hypothesis-testing and falsificationism.
3. Explanationism (holism) ("inference to best explanation")
   - Scientific evidence should be integrated in and contrasted with the totality of our beliefs and knowledge
   - Systematic reviews/meta-analyses ("bread and butter") of EBM

Are There Universal Rules of Evidence? EBM as a Socially Constructed Phenomenon

Another important debate in the philosophy of science revolves around the issues of discovery of the universal rules of evidence that hold valid for all scientists at all times. Is EBM the product of such rules, or is the practice of science a socially sanctioned phenomenon that is determined by prevailing scientific/social consensus?[8] This debate has been mostly informed not by an evaluation of logical structure of scientific methods but by an examination of scientific norms held by scientists throughout different periods in history. Thomas Kuhn, possibly the most influential historian of science, argued that there are no universally valid rules.[55] Rather, rules of evidence are different in each scientific paradigm that, broadly speaking, is restricted to a particular scientific practice at a particular time. When theories, exemplars, and standards of the dominant paradigm of the day cannot successfully answer emerging problems in the field, scientific revolution leads to the adoption of a new paradigm.

In Kuhn's classical account of a paradigm, the emphasis is on paradigm as theory plus pragmatic scientific strategies to answer and investigate questions arising within the context of that theory in the face of scientific experience. In the generation after Kuhn, sociologists of science began to interpret Kuhn in a more sociological vein, seeing paradigms as "forms of life" focusing as much on the ways the organization of scientific work through social norms and roles shaped "patterns of inquiry" as on the internal cognitive features of scientific theories. In this wider sense of the term *paradigm*, there is some merit to the claim that EBM is a new paradigm in medicine. For example, prior to 1962, physicians could treat patients with any substance they wished

to use as long as it was justified by their expert knowledge and/or experience.[64] This paradigm, based on tacit reliance on expert judgment, became increasingly questionable as various health care problems occurred, culminating in the thalidomide disaster that resulted in thousands of pregnant women delivering babies with serious birth defects following use of the drug to combat morning sickness. In the context of our discussion, one could argue that a critical event in the evolution of what was to become EBM occurred in 1962 when an administrative decision (passing the Kefauver-Harris Amendments, which required evidence of effectiveness before a product could be marketed in the United States) designated clinical trials as the only acceptable method to determine if a particular drug can be used in humans. The passage of the FDA law institutionalized knowledge that is publicly shared and easily understood by all qualified professionals in the field who share a common set of the tools and values.[64]

From 1962 to the present, we have witnessed a refinement of the socially institutionalized clinical trial method. Therefore, one can argue that the practice of EBM reflects the development of socially sanctioned standards that arose from the need to get our facts in order.[65] In this sense, social developments have reflected the views that objectivity in science demands that scientific evidence retains its "public character."[30,66] All statements of empirical science must be subject to substantiation by *public evidence*, ie, evidence that can be secured by different observers and does not depend essentially on the observer.[66-68] However, as we will see below, the recent changes in EBM do allow the use of *private evidence* (ie, a unique patient's experience, pain, etc) that is not accessible to multiple individuals, although it still requires that elicitation of that evidence be reproducible.[13]

"For or Against" Method: Is EBM a Democratic or Authoritarian Force?

The insistence that only knowledge that can be understood by everyone who understands methods of clinical research ("the rules of the game") is admissible has been appealing to professionals and the public alike.[64] Some have argued that EBM is a dramatic democratizing force[4] — anyone can challenge anyone. Within the EBM paradigm, students can challenge professors and patients can challenge their doctors. However, a recent critique of EBM has charged exactly the opposite: widely popularized hierarchical rules of EBM have resulted in the stifling of scientific debate and have threatened scientific progress.[7,8] A related and ongoing question relates to the role of experts.[69] Are they best qualified to assess evidence and make recommendations, or does their deep involvement in a topic, often shaped with conflicts of interest,[70] make them unreliable and biased interpreters of medical evidence?

Is there a similar precedent in history of the philosophy of science that reflects this EBM debate? Although the context was quite different, we believe that a debate that occurred between two philosophers of science, Lakatos and Feyerabend,[71] in the 1970s may be illustrative of the issues related to the possibility of identifying the universal scientific method vs the role of individual researchers (experts). While Lakatos maintained that there is a universal scientific method that survives the test of time, Feyerabend warned against "tyranny of method."[72] Feyerabend challenged the scientific community to develop a set of methodological rules, and he claimed he could show that following these rules would have been catastrophic — some important scientific advances never would have occurred.[71,72] There is always an exception to any (methodological) rule. In the context of EBM, all hierarchical rules of evidence are sometimes violated by exceptions. Thus, none of the 106 systems of hierarchical rules of evidence described in the literature completely meet the criteria of reproducibility and logical coherence.[23] The recently developed new system of evidence[17,73] has replaced the original rigid interpretation of evidence, de-emphasizing the hierarchy evidence according to the study design. The latest developments within EBM appear to acknowledge that the universal set of rules that govern medical evidence may not be possible to develop[73] and that there are always exceptions to the general rules described in the EBM systems. Instead, the focus has shifted to transparency and explicitness in interpretation of evidence and making recommendations.[73]

Nevertheless, insistence on the scientific standards can help us defend against false claims and charlatans. However, extending scientific authority to legitimize intellectual authority can represent a "threat to democracy."[72] According to this view, the individual genius of creative thinkers allows them to productively disregard observation in favor of theory or vice versa; institutionalization of a particular scientific methodology is a threat to society.[7,8,72]

Central Role of Evidence

Continuing this debate, we can ask whether society would be better off, on average, by insisting on the set of standards that are socially sanctioned or by relying on the individual geniuses to help us arrive at the truth. Does "anything go," as some post-modernists[72] would have it, or is there such a thing as the objective scientific methodology that can be universally accepted by everyone?[28] EBM espouses those philosophical views that endorse a central role of evidence to serve as a neutral, objective arbiter among competing views, thereby aiming to generate agreement among rational observers.[13] Even if we accept that our observations may be theory-laden, it is incontestable that evidence sometimes overwhelms prior theory and "speaks for

itself," as in the examples illustrated in the introduction. As a result, scientific evidence (at least in some circumstances) has been able to secure objectivity, ie, intersubjective agreement among inquirers who may have held the opposite views.[13,67,68] EBM has embraced the view that "rational thinkers respect their evidence" and that "a wise man proportions his belief to the evidence."[13] Philosopher Bertrand Russell expressed a view dear to the hearts of EBM enthusiasts: "A habit of basing convictions upon evidence, and giving them only that degree of certainty evidence warrants, would, if it became general, cure most of the ills from which the world is suffering."[74]

Criticism of EBM

We have mentioned some of the criticisms of EBM. In general, attacks on EBM have come from five points of view: (1) reductionism in scientific method,[75] (2) a neglect of postmodernist ideas of social importance of science activity,[8] (3) the need to acknowledge patients' values and their subjective experience, as well as physicians' "tacit knowledge" (ie, private evidence) gained through a long practice of medicine,[9,11,76] (4) an inadequate framework for successful problem-solving and decision-making,[10] and (5) lack of the evidence that EBM improves patient outcomes.[77] We would agree that the first and last two criticisms have some legitimacy. As discussed above, we see EBM as a socially constructed phenomenon in terms of Kuhn's (new) scientific paradigm addressing the crisis in the practice of medicine that for centuries has relied almost exclusively on the subjective opinions of experts. EBM offers a new set of habits and ways of practicing medical science (Kuhn's shared sets of values).[55]

EBM's strong elements of reductionism have facilitated a pragmatic approach to clinical problem-solving.[26,78,79] EBM proponents have recognized from the beginning the limitation of inferences from group observations (observed reality) and the need for decision-making to reflect patient values (unobserved reality of phenomenology of experience). In recent years, EBM proponents have placed increasing emphasis on the assessment of the quality of life and the role of patient values in decision-making, thus allowing the use of private evidence in scientific reasoning and decision-making. Nevertheless, despite some recent developments in this direction, EBM has yet to present a fully developed theoretical framework for accomplishing effective problem-solving.[80] Therefore, appealing normative features of EBM are yet to be translated into actual empirical proofs that the practice of EBM will have a favorable impact on patient outcomes. Such proofs are unlikely to arise; the best EBM will ever do is demonstrate that the application of its principles leads to practices that are consistent with the best available evidence (where best is determined by EBM principles).

Conclusions: Going Full Circle, From Observation to Theory and Back

EBM has been shown to be exceedingly useful in clarifying and improving the process of problem-solving and decision-making for individual patients and for populations. For example, today's widespread use of practice guidelines, which represents a quiet revolution in clinical medicine, is a direct result of the EBM movement. However, it is possible that development of a fully articulated theoretical framework would further enhance its usefulness. EBM will continue to emphasize and rely on formal hierarchical rules of evidence, as in the newly developed GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system.[17] However, EBM will continue to acknowledge that there will always be exceptions to the rules.[81] The biggest challenge to EBM continues to be ensuring that decisions are consistent with patient values and preferences. Helping to resolve this vexing issue represents a key frontier of EBM practice and investigation.

Writing 30 years before the term "evidence-based medicine" was coined, Tukey[82] formulated the key challenge for the medical science and practice of medicine: how to move from estimation, with respect for "truthfulness" of evidence, to decisions in specific clinical situations. Clinical problem-solving and decision-making remain at the heart of EBM; the theoretical development that should inform further development of EBM should come from the field of decision sciences.[26,78,79,83] The key challenge that needs to be tackled is how to elucidate a process of optimal decision-making.[84] This includes the difficult task of defining rational decision-making for individuals and society and the application of evidence obtained from group observations at the patient bedside.[84-88]

Our analysis shows that EBM is not about developing a new scientific or philosophical theory. EBM is not designed as a scientific theory, but rather as a structure for optimal clinical practice. It is a different way of practice, and it has become a coherent (if evolving) theory of practice.

This paper is a testimony of benefit that can be derived by connecting people through the Internet. The content of the paper has been shaped by the ideas of people around the world who have freely exchanged their thoughts in contribution to the EBM debate. We particularly wish to thank Roy M. Poses, MD, for his suggestion to work on this paper, which initially started as an exchange of ideas on the EBM discussion group. We also thank Howard Mann, MD, Marit Johansen, BA, DLSc, and Rebecca Kukla, PhD, for critical feedback on the earlier version of this paper. Finally, we thank anonymous reviewers for their helpful and insightful comments.

Competing Interests

Dr Guyatt coined the term "evidence-based medicine" and has been intimately involved in its development ever since. Dr Djulbegovic has devoted a better part of his career to the issues of evidence and decision-making. The authors hope they continue to be open-minded to the topic explored in this paper and that their presentation is fair, balanced, and respectful of opposing views.

Disclosures

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

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Glossary

Abduction: inference to the best explanation.

Consilience: the explanation and prediction of observational phenomena across disciplines.

Deductivism: an epistemological approach based on deductions, a form of reasoning in which conclusions are derived from premises in such a way that conclusions must hold true if the premises are true.

Empiricism: an epistemological view that experience obtained through the traditional five senses is the basis of our knowledge.

Epistemology: the theory of knowledge, the branch of philosophy concerned with the nature of knowledge and its analysis, scope, and possibilities.

Evidence: grounds for belief, "that which justifies belief."

Evidence-based medicine (EBM): a set of principles and methods to ensure that, to the greatest extent possible, population-based policies and individual decisions are consistent with evidence of effectiveness and benefits.

Explanationism: an epistemological approach which holds that some beliefs are justified by inference to best explanation.

Fallibilism: a philosophical doctrine which holds that scientific knowledge is never complete, is always subject to revision, is invariably vulnerable, and may be proven false.

Falsificationism: epistemological approach which holds that scientific testing can falsify but never confirm theories or hypotheses.

Heuristic (often used to indicate heuristic method): "serving to discover," reasoning not regarded as final and strict but provisional and plausible only, whose purpose is to discover the solution of the present problem; use of "rules of thumb" to find solution or answers.

Holism: a view that statements and findings are meaningful only in the context of a whole theory (totality of observations).

Inductivism (induction): an epistemological approach based on induction; a form of reasoning in which inferences are derived from particular to general (ie, from a limited number of observations to wider generalizations).

Inference to best explanation: the range of inferential practices (abduction, explanatory inferences) with the goal to accept the theory that is better supported by evidence than rival theories.

Instrumentalism: the notion that scientific theories are tools for predicting observations and thus do not have to be true to be valid.

Knowledge: traditionally defined as "justified true belief"; the importance of justification varies among different theories of knowledge.

Logical-positivism: the movement in the first part of the 20th century that emphasized a verification principle according to which a statement is meaningful if it either states a logical tautology or is in principle capable of empirical verifiability. (The adjective logical is meant to reflect the application of symbolic logic, while positivism is meant to emphasize the central role of experience in science. The term positive was coined by the French philosopher August Comte [1798-1857], the "father" of sociology, who referred to it as "not speculative, or inferential, immutable basis of fact which compels agreement because it is given prior to the inferences based upon it.")

Operationalism: the view that scientific concepts are synonymous with operations used to measure them.

Private evidence: the subjective character of a claim that is known only to specific individuals and is not accessible to multiple individuals.

Public evidence: the public (objective) character of evidence which indicates that evidence can be secured by different observers and does not depend essentially on the observer.

Rationalism: an epistemological view which holds that reason alone rather than empirical observation can be a source of knowledge.

Tautology: necessary truths (logical tautology refers to a statement that is true in every circumstance).

Theory-ladenness of observations: the view that all observations are interpreted through the medium of theories.

Underdetermination: generally understood as underdetermination of theory by evidence; the view that for any given set of observations, more than one theory can be shown to be logically compatible with the evidence.