Evidence-Based Medicine

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Abstract

Evidence-based medicine (EBM) is a science in itself which paves way for effective utilization of healthcare literature in medical practice. EBM is not only about overcoming subjective judgment, tradition, and authority in medical practice, but to impart other values such as patient preferences and choices along with best-available evidence. Hence, EBM can be considered as a "patient-centred" approach to clinical decision-making. Currently, EBM lies at the core of clinical practice. EBM tends to integrate "clinical epidemiology" and "biomedical research" – by imbibing and applying their concepts, "statistical analysis" and "scientific methodology", respectively. The real purpose of EBM was to harness the incremental increase in biomedical data and ever-expanding medical knowledge – with far few "real" breakthroughs – and make the "busy" clinicians to adopt and implement the "best" available evidence efficiently in day-to-day clinical practice. Initially, EBM was essentially focused on three major domains, namely, critical appraisal of available literature, development of systematic reviews, and clinical practice guidelines. All along these years, it is observed that EBM had contributed heavily to clinical medicine in the following ways, as quoted by Guyatt *(the scientist who had introduced the term "Evidence-Based Medicine", 35 years ago)* himself, shifting the practice of medicine on the base of scientific judgement, delineating the complex evidence hierarchies, prioritizing the patient values and preferences in clinical decision-making, and in the development of more robust methodologies for producing trustworthy guidelines and recommendations. In this chapter, the definitions, evolution, current status, progress, and future of EBM are deliberated extensively.

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A. Arivazhahan et al. (eds.), *Introduction to Basics of Pharmacology and Toxicology*,
https://doi.org/10.1007/978-981-95-1920-0_4

Keywords

Evidence-Based Medicine (EBM) · Evidence-Based Practice (EBP) · Critical appraisal · Evidence pyramid · GRADE (Grading of Recommendations, Assessment, Development, and Evaluation system) approach · Evidence-Based Clinical Practice (EBCP) · PICO · Shared-Decision-Making (SDM) · Cochrane collaboration

> The first two years of medical school have got to be changed. Students are spending more and more time understanding the difficult aspects of molecular biology, but we are kidding ourselves to think they use their knowledge of DNA – in my day it was the Krebs cycle – in making clinical decisions at the bedside. They do not. They make clinical decisions based on how the last patient did, how their friends are treating patients and what the latest article by an authority says they should do. And we have got repeated evidence now that authorities are way behind with regard to the data in clinical trials – Dr. Tom Chalmers (1993)

> Half of what you'll learn in medical school will be shown to be either dead wrong or out of date within five years of your graduation; the trouble is that nobody can tell you which half—so the most important thing to learn is how to learn on your own – Dr. David Sackett (2003)

> Evidence-Based Medicine was ranked 7th among the top 15 most important medical advances (innovations) in healthcare since the journal's inception in 1840 – BMJ (2007)

> Research that leads to neither new insights nor new applications is wasted. Research that is poorly done is wasted. Research that nobody reads is wasted. Research that has been done before is wasted – Sir Iain Chalmers (2009)

4.1 Introduction

Evidence-Based Medicine (EBM) is rightfully placed alongside the discovery of antibiotics and vaccines as one of the most significant medical advances in the past 150 years. It can be considered as a strategic alliance between medical science and clinical experience for a more modern and ideal application of clinical practice. The basis behind EBM is to guide clinical practice by systematic biomedical research. In literal parlance, EBM can be considered as "medicine practiced on the basis of evidence".

The term EBM is sometimes referred to as "evidence-based practice (EBP)", "evidence-based clinical practice (EBCP)", or "evidence-based healthcare (EBHC)".

4.1.1 Evidence-Based Medicine—*The Definitions*

Evidence-Based Medicine can be defined as "the conscientious, explicit, and judicious use of current best evidence from healthcare research in making decisions

about the care of individual patients and populations". Here, "evidence" (scientific) is "the evidence that serves to either support or counter a scientific theorem or hypothesis" *[Encyclopedia of Public Health]*.

The above definition of EBM was put forth by Sackett et al in 1996. In this paper, Sackett et al state that practising EBM entails the integration of "individual clinical expertise" with the "best available external clinical evidence (from systematic research)"—what they refer to as the "bottom-up" approach. And both these tenets are not mutually exclusive—i.e., a good doctor needs to use both. Hence, Sackett wanted integration of systematic research with expert judgement.

As per the above definition, the practicing physician must keep himself abreast with the current relevant research and should continuously seek for the optimal course of care for the patients under his treatment. Hence, EBM can be considered to possess the following characteristics: "explicit search for the best evidence", "fair judgment for the benefit of the patient", "complementary participation of patient in the decision-making process", and "gradual practice-based fine-tuning of clinical experience"). By this way, EBM keeps the stakes of all participants of healthcare delivery at ideal levels—for the physicians, EBM reduces the chances of committing errors; for the patients, EBM provides opportunity to self-contribute in the process that deals with their own life; and for the payers, EBM instills a sense of certainty and surety. Hence, the practice of EBM demands the integration of individual clinical expertise with the best available external clinical evidence generated from systematic research along with the patients' values and preferences (Fig. 4.1).

And the BMJ Best Practice defines EBM as, "the application of the best available research to clinical care, which requires the integration of evidence with clinical expertise and patient values". The best available research refers to clinically relevant (i.e., patient oriented) research that: illuminates the accuracy and precision of diagnostic tests; highlights the importance of prognostic markers; establishes the efficacy and safety of therapeutic, rehabilitative, or preventive healthcare strategies; or seeks to understand the patient experience. Hence, it is the physician-patients' values, preferences, concerns, expectations, circumstances, and settings that dictate the administration of the best available care—hence, EBM is not so-rigid as it is construed and always looks for the "best-tailored fit" in therapy for the individual patient.

And sometimes, EBM is considered as a combination of three components, namely, "clinical state and circumstances", "patients' preferences and actions", and "research evidence"—in that order; and the integration of the "physician's clinical expertise" with all of the above three components—as the fourth element.

The basic elements of EBM include (i) framing (defining) a clinical question—the four components of which are the "PICO: patient (or population), intervention (or exposure), comparison (or control), outcomes"; (ii) finding (searching) the best available evidence—MEDLINE (accessed through PubMed), Embase, and CINAHL are some of the notable medical research databases comprising millions of references to journal articles; (iii) assessing the certainty (quality) of the evidence—which includes ascertaining both internal validity (bias or "systematic" error and chance or "random" error) and external validity (generalizability); and (iv)

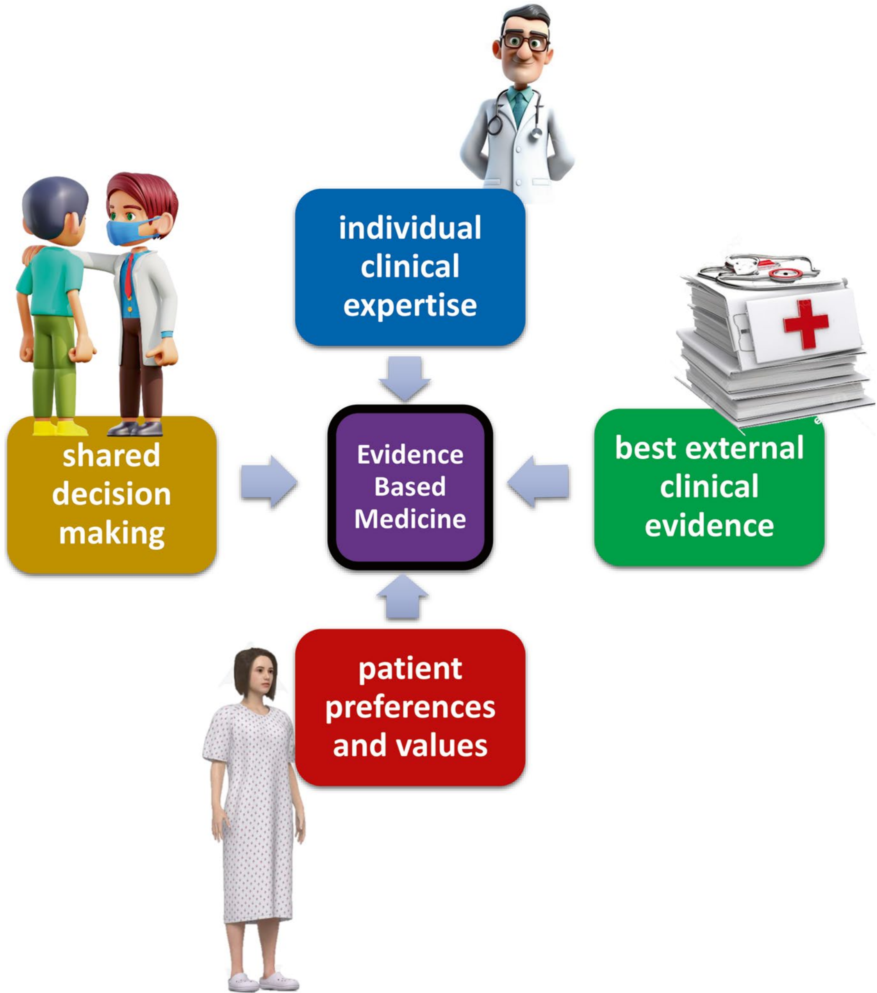

Fig. 4.1 Components of evidence-based medicine (EBM)

applying the evidence in practice, along with complementary clinical expertise and patient preferences—acting on the evidence to make a clinical decision. By following this framework in a sequential order, the EBM cycle comprises the following steps, namely, (i) "Asking" the question, (ii) "Acquiring" the evidence, (iii) "Appraising" the evidence, (iv) Incorporating "patient values and preferences", and (v) "Applying" to the patient. And this practice framework was put forth by Sackett himself in 1997. He also added that "the practice of EBM is a "process of life-long, self-directed learning" in which caring for our own patients creates the need for clinically important information about diagnosis, prognosis, therapy, and other clinical and healthcare issues". The above discussed "Sackett process" involves the

following steps, namely, (1) structure a researchable question, (2) select the most likely resource, (3) design an effective search strategy, (4) summarize and critique the evidence, (5) apply the evidence to the patient of interest, and (6) evaluate the process and outcome.

UpToDate® (Wolters Kluwer), DynaMed® (EBSCO), ClinicalKey® (Elsevier), and Essential Evidence Plus (Wiley) are some of the notable point-of-care EBM tools which support in clinical decision-making for healthcare professionals.

The application of EBM in actual clinical practice requires a series of focused efforts and the "scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services and care" is referred to as the "implementation research". Sometimes, also denoted as "implementation science"—which "aims to accelerate the adoption and integration of evidence-based practices, interventions, and policies into routine healthcare and public health practice to improve the impact on population health". Hence, through implementation science the gap between research and practice can be abridged.

Ultimately, by application of EBM, the healthcare delivery becomes better, safer, and cost-effective. And EBM can also be considered as "an evolutionary progression of knowledge based on the basic and clinical sciences and facilitated by the age of information technology".

4.2 Evidence-Based Medicine—*The History and Evolution*

The term Evidence-Based Medicine first appeared in an editorial (1991) by Dr. Gordon Guyatt. In that single-author paper, he describes that EBM requires skills of "literature retrieval", "critical appraisal", and "information synthesis". Hence, additional strategies like quickly tracking down publications of studies that are directly relevant to the clinical problem, critically appraising these studies, and applying the results of the best studies to the clinical problem at hand are the crucial steps in EBM. He also goes on to add that EBM requires judgement of the applicability of evidence to the patient on focus and follow systematic approaches to make decisions when direct evidence is not available.

And in "The Rational Clinical Examination" series in *JAMA* (1992), the Evidence-Based Medicine Working Group discoursed that the EBM as a new approach in teaching the practice of medicine. A paradigm shift from "purely" expertise-based, content (knowledge)-oriented, or clinical experience-based medical practice to more systematic assumptions (observations)-based, critical review of current medical literature, and application of rules of evidence before embarking on diagnostic/therapeutic options on a case-to-case basis was proclaimed. It is also stated that critical appraisal of literature is not merely an academic exercise rather it forms the crux for practical implementation of EBM. And further, critical appraisal would be the new way of doing medical practice by moving it to bedside.

Twenty years later, in an interview for *JAMA Network*, Dr. Guyatt fondly recollects the initial name coined for "evidence-based medicine" as "scientific

medicine"—which then (early 1990s) created a huge uproar among the basic medical scientists and was not received well.

And Dave Sackett recollects how the term "critical appraisal" was requiring the much-needed rechristening to "evidence-based medicine"—as it involves science and literature integrated with best clinical skills to get the diagnosis right. So, EBM is a more broader term than critical appraisal—and it also involves evidence in the context of patient values and preferences.

And often, alignment with patient priorities with regard to clinical decision-making in care delivery has done wonders in improving healthcare outcomes. This process of "Shared-Decision-Making (SDM)" is now considered as a distinct entity in medical practice evolving from the roots of EBM. In SDM, the patient becomes the centre of clinical activity and this recent transformative collaboration of patients with doctors is referred to as the "patient revolution" in medical practice. The Mayo Clinic has even released freely accessible tools in the public domain for ready implementation of SDM; as actual implementation of SDM is generally considered as tough and challenging.

4.2.1 The Cochrane Collaboration and Archie Cochrane

Ian Chalmers was the forerunner for the establishment of the Cochrane Centre in Oxford (UK) in 1992 which was later transformed into The Cochrane Collaboration. Cochrane is an international independent network of researchers and healthcare professionals that perform systematic reviews of the evidence. These systematic reviews are high-quality literature reviews (unlike the narrative reviews) performed using systematic methods and are referred to as the "Cochrane Reviews". The Cochrane Reviews and the protocols for Cochrane Reviews ("Cochrane Protocols") can be retrieved through the *Cochrane Database of Systematic Reviews (CDSR)* which is a key component of the Cochrane Library. As on date, the CDSR includes more than 9000 Cochrane Reviews and stands as the leading database for systematic reviews in healthcare.

Cochrane recluses itself from commercial funding and is a not-for-profit organization with over 50 thousand collaborators (including patients, carers, and anyone interested in improving health outcomes) originating from more than 190 countries. And currently, the cochrane.org can be accessed in 20 different languages. The flourishing of The Cochrane Collaboration is a testimony for the perceived need to utilize EBM by healthcare professionals.

The stalwart epidemiologist Archie Cochrane was a fervent patron for conduct of randomized controlled trials (RCTs) despite the then accusations that were raised by medical ethicists against RCTs. He went on to reaffirm that good controlled clinical trials should replace other pseudoscientific studies undertaken by drug industry. Thanks to the positive influence from his mentor Sir Austin Bradford Hill (the great biostatistician) at the London School of Hygiene and Tropical Medicine—who had performed one of the first RCTs in medical history. He was also fully onto maintaining 100% response rate in epidemiological studies and even coined the

self-eponymous term, namely, the "Cochrane units"—one Cochrane unit refers to a response rate of 91%, two Cochrane units refers to a response rate of 95%, and so on.

Cochrane's 50-year-old treatise titled *"Effectiveness and Efficiency: Random Reflections on Health Services* (1972)*"* discourses about "effectiveness" ("confirmed benefits of healthcare interventions – preferably by RCTs"), "efficiency" ("optimal delivery and utilization of available health resources for achieving positive outcomes"), and also about "equity/equality" ("assessment of the variation in healthcare delivery") in healthcare services. The book had a resounding reception and was later translated to eight languages. He also emphasized the need for systematic and scientific collation of all available RCTs ("critical summary"). He had assumptions on the concepts of cost-effectiveness and cost-benefit too (extension of the "effectiveness" component). And the setting up of The Cochrane Collaboration by Iain Chalmers and his colleagues in 1993 was a fitting tribute to the scientific envisions of Cochrane. And the Cochrane Collaboration was perceived on par to the Human Genome Project in its potential implications for modern medicine.

Medicine continues to be an undiscernible mixture of "science" and "art". EBM, in a way, helped in transcending the branch of Medicine away from its "uncertainty" and "probability" qualms—as Sir Willian Osler quoted medicine as a science of uncertainty and an art of probability.

However, there are some arguments speculating against the evolution of EBM like—EBM is not only about the RCTs as deciphered through the Cochrane's book and the confines of EBM should not be as narrow and restrictive as it is construed. Moreover, the reliance on the RCTs and the database of systematic reviews (including that of the Cochrane Collaboration) should not override the facets of clinical intuition and care dimension of clinical work including to bank on more humanistic doctor-patient relationship ["no RCTs, no real scientific evidence"—is false]. And RCTs should not only be considered as the universal gold standard of medical evidence but rather as means of detecting ineffective treatments; and consequently, redirecting the cost-saved to improve the healthcare system as a whole. It is emphasized that the "quality of care (living)" is equally important as that of the "quality of treatment" if not more. And also, the "recuperative power of the human body" should never be underestimated compared to the existing "therapies". This reverting back to "traditional" aspects of healthcare was even referred to as the "renaissance" movement of clinical practice—by the critics of EBM. The critics also go on to add that EBM is trying to "purify" medicine by letting out the "care" aspect of medicine and rather focusing more on the "scientific cure" part of medicine ("curative medicine").

In line with the motto of "critical appraisal" or rather forthright "criticisms" of scientific evidence and also doubled up with direct onslaught on some of the lacunae of the Cochrane Collaboration, the Collaboration itself came up with an innovative award, namely, the "Bill Silverman Prize". The award is given annually to the individual with the best critique "either through evaluating any aspect of the preparation, maintenance or dissemination of Cochrane Reviews or about the work of Cochrane more generally". Bill Silverman was a paediatrician who always asserted that, "criticism (including self-criticism) is a form of troublemaking that can help to

drive progress"—hence, it is implied that, "all criticisms are helpful, and there are no such thing called 'negative' criticisms".

Like some philosophers who state that "evidence" in EBM (medical practice) should be viewed differently to that of the "evidence" in medical sciences—as the former is an exercise of identifying "something meaningful for someone" (e.g., in clinical decision-making) and the latter is an exercise of identifying "a sign of something" (e.g., in a scientific inquiry).

And even after two decades of its inception, there is wide variation in the implementation of EBM. Even now, it is sometimes emphasized that evidence that led to EBM should be considered only in the context of the patients—and not as a sole approach. This context is derived from the experience of practitioners—both individually and collectively. Hence, it is stated that EBM needs to complement experience-based medicine (ExBM) and can be more appropriately called as "Evidence-Informed Care".

Nevertheless, EBM is built on the base of conventional medical training and skills which includes a strong background of understanding of pathophysiological principles, meticulous history taking and physical examination, and also the need for compassionate attitude of the physician towards his/her patients.

4.3 Progress and Current Status of Evidence-Based Medicine

The proponents of EBM faced the brutal backlash from *The Lancet* anonymous editorial (1995) which scathingly stated, "…we deplore attempts to foist evidence-based medicine on the profession as a discipline in itself…". The editorial also rebuked the statement proclaimed by the EBM-group during the launch of the new *Evidence-Based Medicine* journal – "publish the gold that intellectually intense processes will mine from the ore of about 100 of the world's top journals". Of the many responses to this editorial, the notable ones are, how "one-way" consultant rounds would be transformed with "two-way" learning-cum-teaching at the bedside; compensate for the lack of time by busy clinicians in critically searching and appraising medical literature ("a general physician would need to examine 19 articles a day, 365 days a year, just to keep abreast of that specialty"); medical knowledge (evidence) should be based on scientific discourse and not on expertise—the former is "democratic and open to debate" and the latter would be "oligarchic and closed"; deficient scientific reasoning by the exponents of EBM—it is not about "choosing adjectives" or "prophesizing"; the advocates of EBM tend to be arrogant and denigrate the alternate views of others; "systematic observation" is not new to medical training, the same was existent since the times of Osler, Virchow, and Koch; in line with Godel's incompleteness theorem, EBM is "built on some shaky logical foundations: it will always be incomplete". Truth will not be contained in a recipe book; and unlike Archie Cochrane himself, "the Cochrane collaborators sit comfortably at their desk reviewing endless studies". All these views revealed the then prevailing ambiguity around EBM.

EBM was initially considered as a threat to “physician’s autonomy” and was even adjudged as a new way of “dogmatic authoritarianism” originating from the Cochranian Oxford (like in parlance from the erstwhile Galenic Rome). But later, rather it disentangled the then plaguing “clinical freedom and democracy” for “evidence-based clinical practice”—as yearned by Cochrane himself.

And some scientists consider “evidence” as a weaker definition of actual “truth”—and as such evidence is only a reason or support for an opinion and not based on actual knowledge-derived “proof”.

Further, EBM was assumed to concentrate only on the rationing of healthcare and equitable distribution of available facilities thereby aiding in cost-cuttings—so EBM had the negative monicker of “rationed medicine” rather than “rational medicine”. One more argument is EBM is shifting focus “from the bedside to the medical libraries or computer terminals”. And as it always said that “statistical significance” does not equate to “clinical significance”—similarly, EBM’s initial “big” gains of the low hanging fruits have now been relegated to only “marginal” benefits in clinical practice.

Then, it was also a general impression that most of available literature (evidence) were for individuals with single isolated conditions and not for the complex comorbidities which are more prevalent. And the developed evidence-based guidelines are often mapped poorly to complex multimorbid states. Additionally, as much of the evidence is not disseminated through formal peer-reviewed publications, hence, we are forced to rely on biased irrelevant evidence for complex disease states.

Even in the introductory paras of the *JAMA* (1992) EBM paper, it was emphasized that neither mere intuition, unsystematic clinical experience, nor sole pathophysiological reasoning should be considered for clinical decision-making; rather, EBM entails the evaluation of evidence from existing clinical research. The same principle holds true even today and skillsets proclaimed then—like efficient literature searching and application of predefined rules in evidence assessment—are indispensable for any practicing clinician of today’s era.

Initially, the EBM Working Group had asserted that only two set of populations (among healthcare providers) could take on application of EBM in clinical practice; one would be those who are overtly convinced about the positive outcomes of EBM on patient care and the other would be those who are quite sceptical about the intended benefits of EBM but even then, they still believe that EBM would not largely deteriorate patient health. The Working Group also concluded that the implementation of EBM would also aid in countering the exploding barrage of medical information, harnessing new technologies, controlling healthcare costings, and ultimately improving quality of medical care.

The “quality seal” embossed on the evidence-based medicine is sometimes misappropriated through vested interests—what is sometimes referred to as the “hijacking of EBM”. Some arguments against the development of evidence-based practice are that most of the evidence is generated through trials funded by for-profit pharmaceutical companies. And the industry’s selective publication of positive results over and above the negative results had been reported on multiple occasions [“publication bias” or “selective (non-) reporting bias”]. All these point towards a more of

a "finance-based medicine" compromising the sanctity of EBM. Hence, the authenticity of such studies is always questioned and the necessity for more academia-funded studies are encouraged. In their pursuit to restrain the participation of the money-minting pharma and maintaining utmost ethical rigor for conduct of clinical trials, Sackett and Oxman satirically proposed (in the *BMJ*) for a company named the "HARLOT plc"—what they confess that would achieve positive results without lying in the fields of biomedical research—by merging the oldest and the second-oldest professions in the world. They wittingly state that through this company "we can protect your worthless product ("drug") as we shepherd it through the mine-fields sewn by objective scientists, fussy ethics committees, conscientious journal editors, writers of evidence-based guidelines, and licensing bodies".

The practice of EBM in the surgical fields is even more difficult compared to that in medical specialities. And the surgeons, in general, were all the more sceptical in the practical feasibility of application of EBM in surgical practice. Previously, lack of well-controlled trials in evaluating various surgical interventions and disinterest from funding bodies (particularly from the for-profit agencies) were considered as hurdles in generating hard evidence in the surgical specialties and hence, compromising on the "quality" of the evidence generated. In the start of the twenty-first century, only about 7% of the surgical interventions were found to be assessed in a randomized study design. The "IDEAL recommendations" was one such approach proposed to improve surgical evidence—which stand for Stage 1: **i**nnovation, Stage 2a: **d**evelopment, Stage 2b: **e**xploration, Stage 3: **a**ssessment, and Stage 4: **l**ong-term study. However, in the past two decades (i.e., 1999–2009 and 2009–19), the number of surgical interventions being evaluated through RCTs has greatly increased. Despite the increase in the quantity and quality, the ethical and logistic issues surrounding the conduct of these (surgical) RCTs still exist. And the inherent practice variability among the surgeons is another concern. Hence, the process and application of "evidence-based surgery" are far more intricate than the practice of EBM.

From the 1988 Commentary in JAMA (the year of passing of Cochrane) which envisaged the advent of "new Cochranes" in the field of medical practice (in the Americas)—echoing the need for well-tested and validated health services interventions, EBM as a whole has metamorphosed to such an extent that clinical practice without evidence is futile.

In the pre-EBM period, it is a usual assertion that the physicians practice only 10% of what they know. This sentence underlines the difficulty of putting EBM into actual practice. In the initial period of EBM establishment, there was an outcry that the contents in the drug label—particularly the so-called "contraindications" were given more weightage despite the inherent lack of strong evidence based on which they are brought out. Further, the practicing physicians were in a way coerced to strictly adhere to these label "contraindications" rather than on best-available evidence and/or patient preferences. All the more there is lack of publications of studies with the so-called "negative" results/conclusions—therefore the available evidence becomes biased. Hence, from the above discussion, it is pertinent that systematic reviewers are at the mercy of researchers of primary studies (RCTs and

others). Therefore, it is the sole responsibility of the primary researchers to undertake trials with utmost care and make systematic reviews and meta-analyses more credible; otherwise, we may land up in the infamous "garbage-in, garbage-out (GIGO)" phenomenon.

"Drugs don't work in patients who don't take them", as opined by Everett Koop in the 1980s, was troubling the implementation of EBM. Nearly 30 to 50% of the patients do not take their prescribed medications and as such even with availability of hard evidence the delivery of appropriate healthcare is at abeyance. And what is even more disheartening is that clinical trials (including RCTs) are marred with compromised medication adherence—i.e., nearly 50% of trial participants do not comply with the dosing regimens specified in the study protocol. Consequently, the evidence generated is also at stake.

The process of making scientific peer review (of biomedical publications) more robust and credible and more so the registering of clinical trials prior to their commencement would make the evidence garnered more accountable. Peer reviewing system is the backbone of medical advances and registries would aid in reducing publication bias ("non-reporting of negative studies"). The "International Peer Review Congress"—which is held every 4 years and the "International Clinical Trials Registry Platform (ICTRP)"—which is maintained by the WHO, are testament for this affirmation.

Not all evidence that is being generated are equal and there are different levels of evidence. Fig. 4.2 illustrates the evidence hierarchy pyramid—wherein controlled biomedical research is placed at a higher level of evidence and compared to information generated from other sources. And some critics say that, in contrast to EBM, for achieving the goals of "precision medicine" the hierarchy of evidence pyramid must yield to a "more horizontal conception of medical knowledge". In precision medicine, the "individual treatment effect" *(patient-centred)* is considered to be more important compared to EBM which relies on the "average treatment effect" *(population-level)*. Whereas some state that "precision medicine" itself is a spinoff of EBM—and the final healthcare model should be rather a unified pluralistic approach with "evidence-based precision medicine". And a novel "medicine-based evidence (MBE)" approach was also proposed—wherein an archive of different patient profiles would be built up and a treating physician could match his current patient with those in the archive and contemplate managing on similar ways based on the accumulated evidence base.

Further, a "6S Hierarchy of Evidence-Based Resources" is suggested for searching and retrieving evidence for guiding clinical decision-making. The model recommends six layers of evidence sources, namely, ***S**ystems* (Computerized Decision Support Systems), ***S**ummaries* (Evidence-based clinical practice guidelines or textbooks), ***S**ynopses of **S**yntheses* (Evidence-based abstraction journals, Database of Abstracts of Reviews of Effects [DARE]), ***S**yntheses* (Systematic reviews), ***S**ynopses of Studies* (Evidence-based abstraction journals), and ***S**tudies* (Original journal articles)—and hence, to proceed from the top to the bottom. The 6S approach can be considered under three broad categories, i.e., the "Systems" and the "Summaries" can be considered under "Summaries and Guidelines", the "Synopses of Syntheses",

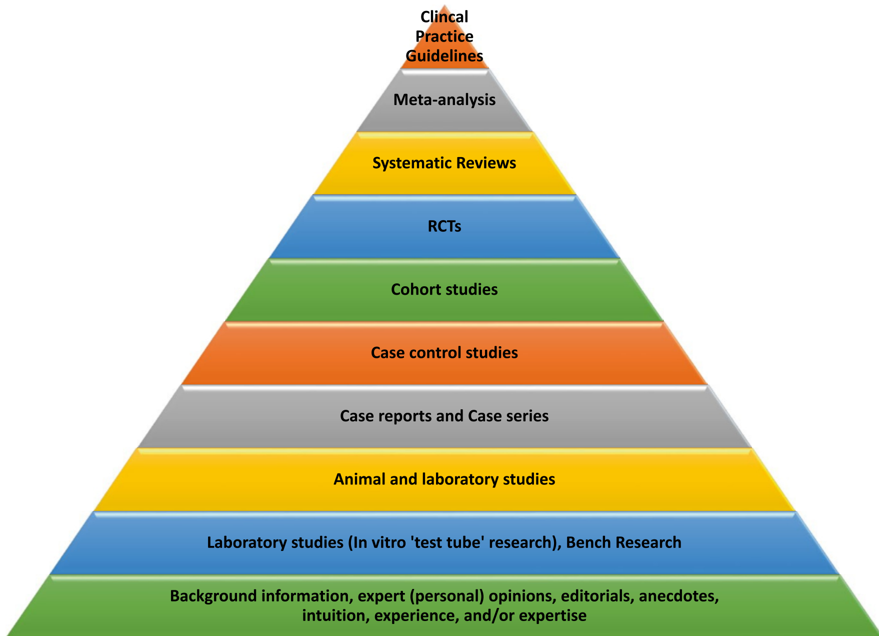

Fig. 4.2 The evidence hierarchy pyramid

“Syntheses”, and “Synopses of Studies” can be considered under “Pre-Appraised Resources”, and the “Studies” can be considered under “Non-Appraised Primary Studies”. The TRIP (Turning Research into Practice) (www.tripdatabase.com), Epistemonikos (https://www.epistemonikos.org/en/), and ACCESSSS—Access to Evidence-based Summaries, Synopses, Syntheses, and Studies (https://www.accessss.org/) are some of the metasearch engines available for retrieving evidence from multiple levels of resources.

4.4 Future of Evidence-Based Medicine

The concept of EBM is easily one of greatest revolution in clinical practice of modern medicine and the *New York Times Magazine* hailed EBM as one of the most influential ideas of the year (2001). And for like any sudden shift in medical practice, EBM was initially fraught with scepticism among physicians, medical students, patients, and others. The acrimonious sobriquet “cookbook medicine” was tagged to EBM—where EBM was considered alike the recipe books and to be followed verbatim in spirit and letter (“slavish”). And even some referred to it as “ego-based medicine”.

Previously, time constraints and ready access to latest medical literature were considered as some of the barriers to implementation of EBM in actual practice. However, with the advent of cutting-edge information technology systems these

impediments have been cut short. And real-world studies have categorically proven that evidence-based practice improves patient outcomes and physician performance compared to the conventional standard practice.

In the Americas, the incorporation of evidence-guided medical decisions (EBM) was considered as the “fourth revolution” of healthcare following “introduction and expansion of health insurance”, the “backlash of payers to reduce costs”, and “outcomes-based research”.

Like when Guyatt in his seminal editorial paper on EBM mentioned that clinicians need to look beyond the expertise of an expert lecturer or a local senior physician, or a textbook (compiled sometime back) to resolve patient management issues—hence, like the transition from “authoritative expertise-based medicine” to “evidence-based medicine”, the onus lies with the clinicians to keep all the senses wide-open to imbibe further rational transformations of this discipline.

The spread of EBM and its applications to multiple disciplines of medical sciences showcases the broader impact of EBM. EBM, like discussed above, is a decisive tool to bring in social justice and health policy making.

The overconcentration of EBM on drugs and devices has left the other areas of healthcare in an “evidence vacuum”—and hence, more and equal evidence needs to be generated in the areas of health policy, health management, and health reforms.

EBM has progressed by leaps and bounds although it be with some expected hiccups; similar to how Cochrane had to struggle in executing his first “randomized” and “controlled” trial (1941) *[what he states as his first, worst, and most successful clinical trial]*, the successful accomplishment of the RCT on aspirin in secondary prevention of mortality in post-MI patients, and ultimately, culminating in the inception of the Cochrane Collaboration (1993).

As of now, though RCTs are considered as the “gold standard” of all clinical study designs in assessing therapeutic effectiveness, we could expect a change of views with inclusion of better type of trial methods—hopefully! And recently, it has been noted that, “on average, the effect estimates of RCTs and observational studies differ only very slightly”. Hence, it is not only about the study design, i.e., RCTs vs other observational study designs (including retrospective and prospective cohort, case-control and cross-sectional studies).

As Gordon Guyatt envisages the need for highest level of easily accessed, easily understood, and preprocessed evidence is more than a basic requirement currently considering the burgeoning medical literature. More than 23 million articles published in over 5600 medical journals in the past 40 years; and around 25,000 to 30,000 randomized trials are being published every year in the last decade—what is referred to as the “bibliometric explosion”. And a study in 2010, reported that 75 RCTs and 11 systematic reviews are being published every day. However, the good news is that a clinician needs to be aware of only 20 new articles per year to keep himself up to date in his area of expertise.

And Guyatt goes on to add that how succinct evident summaries (along with underlying patient preferences and values) of Standard Treatment Guidelines (STG) would come in handy for a busy primary care practitioner. The generated evidence is translated to applicable recommendations. The introduction of the “Grading of

Recommendations, Assessment, Development, and Evaluation (GRADE) system" is one such approach (a science for guidelines-making) for developing and presenting summaries of evidence ["quality or certainty of evidence"] and providing a systematic approach for making clinical practice recommendations ["strength of recommendations"]. This GRADE approach has been adopted by over 100 organizations—including the WHO and the NICE (National Institute for Health and Care Excellence, UK). And the Appraisal of Guidelines, Research and Evaluation (AGREE) Instrument is another such tool to assess the process of guideline development and reporting. Hence, a "trustworthy" clinical practice guideline should not only show the direction ("for" or "against") but also needs to quantify the strength ("strong" or "weak") of the provided recommendations.

Further, it should be noted that the generated evidence-based guidelines are not mere hard-fast directives and are not supposed to be overtly prescriptive—rather they should be considered as "guidance" document to a practicing physician. All guidelines and recommendations should only be considered in light of the relevant local factors that were involved by the guideline panel. So, while we need to "globalize the evidence", we need to "localize the recommendations". And the focus on EBM is getting rightfully shifted from more of a sphere of academic excellence yearning for the "ideal evidence" to implementation research, knowledge translation, and shared decision-making.

There are different critical appraisal tools for quality assessment of studies, such as the JADAD scale or the Revised Cochrane risk-of-bias (RoB 2) tool for "randomized trials" and the Newcastle-Ottawa Scale (NOS), Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I), or the Methodological Index for Non-Randomized Studies (MINORS) for "non-randomized studies". And the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews—2) critical appraisal tool can be used for "systematic reviews" that include randomized or non-randomized studies of healthcare interventions, or both. Additionally, critical appraisal checklists are being provided by the Critical Assessment Skills Programme (CASP) which was started (1980s) with prime objective of getting research into actual practice.

Currently, the "narrative reviews" are less relied upon and for obvious reasons the "systematic reviews" (and in some cases, "scoping reviews") have become more credible for evidence generation—what is sometimes referred to as the transformation from "eminence-based medicine" to "EBM". As the "narrative descriptive reviews" are generally written by the so-called subject experts and hence, are largely influenced by the expert's perception, experience, and also bias. In the beginning, to perform a systematic review it took nearly 2 years and now the same has been fast-tracked and the execution time is cut-short to almost by 75% (6 months) and sometimes, even to 2 weeks (by using automation tools); and the pioneers of EBM are quite confident that systematic reviews would be completed in a matter of 2 minutes in the near future. The Systematic Review Accelerator (SRA) is one such tool developed for the same purpose by Paul Glasziou and his team from the Bond University.

As expected, EBM is becoming more complex with the proposals such as the "next-generation 'deep' evidence-based medicine" which incorporates the various

facets of advanced digital technologies (including machine learning and deep learning components), biomarkers, real-world data, and also out-of-the-box clinical trial designs. Study designs such as basket (or bucket) trial, umbrella trial, platform trial (e.g., the Recovery Platform Study), and master observational trial (MOT) [a combination of the master interventional trial and prospective observational trial] are being explored which could drastically cut short the time, efforts, and cost involved in development of novel drugs. And recently, the large language models (LLMs) such as ChatGPT have been found to accurately and consistently predict the RoB assessment of RCTs.

Table 4.1 enlists the contributions made towards EBM by some of the stalwarts of EBM.

4.5 Conclusion

Let us say no to "GOBSAT"— "Good Old Boys Sat Around the Table"—a process by which many guidelines were in fact developed previously—wherein a set of self-proclaimed subject experts discuss their often-subjective biased opinions and pontificating the same which may boil down as "consensus statements" or "expert opinions".

Ever since EBM was taking foothold, the transition of centre stage from treating physicians to care-receiving patients was highly perceptible. It is not only about how "clinicians" access, evaluate, and interpret the existent medical literature but also how this rigorous systematic exercise transforms "patient" lives. And it is a known fact that not all medical queries are always answered leading to implied uncertainty in clinical practice. In this context, EBM helps to maintain the much needed equipoise in patient care by providing extra cushion in acknowledging the dearth in current existing knowledge and how to tackle the same diligently. So, EBM not only considers high-quality evidence but also gives equal weightage for lack of robust evidence (low-quality evidence).

As it was discussed earlier, the healthcare of the twentieth century was more from the "doctors" (physician-centric) whereas from the start of the twenty-first century the attention has shifted towards the "patients" (patient-centric; *"no decision about me without me"*) and presently, the focus is on how to mutually consider each other's inputs so as to attain optimal therapeutic outcomes—"participatory medicine".

Like how Cochrane admonished against "God complex" as a terrible affliction of the then physicians—which is an absolutely overwhelming belief that their solutions to complex medical conditions are infallibly right, we need to move from this complex to a more "Human complex" (as the term indicates, humans are prone to errors and less autonomous) but rather with a "divine touch" (the thirst for an "ideal" state). Thanks to EBM—which rightfully embraces uncertainty with available evidence on par with good quality evidence—and hence, pushes for accruing more evidence!

Table 4.1 Pioneers of evidence-based medicine (EBM)

Name	Notable Affiliation(s)	Contributions and Accolades
Sir Austin Bradford Hill (1897, London, England –1991, Cumbria, London)	Reader, Epidemiology and Vital Statistics, London School of Hygiene and Tropical Medicine (LSHTM) Dean, LSHTM Chair and Director, Statistical Research Unit, Medical Research Council (MRC) Secretary and President, Royal Statistical Society	Hill's criteria for causation Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300. https://doi.org/10.1177/003591576505800503 First scientist to prove a correlation between cigarette smoking and lung cancer (along with Richard Doll) Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J 1950;2:739–748. https://doi.org/10.1136/bmj.2.4682.739 Introduced randomization; pioneered the first modern RCT (use of streptomycin in treating tuberculosis) Hill AB. Principles of Medical Statistics. London: Lancet, 1937 Book: *Bradford Hill's Principles of Medical Statistics* *Honours:* Guy Medal in Gold (1953) Harben Gold Medal of the Institute of Public Health and Hygiene Commander of the Order of the British Empire (CBE)
Archibald (Archie) Cochrane (1909, Galashiels, Scotland—1988, Dorset, UK)	David Davies Professor of Tuberculosis and Chest Diseases, Welsh National School of Medicine (University of Wales College of medicine), Cardiff, Wales Director, Epidemiology Research Unit, UK Medical Research Council (MRC), Cardiff, Wales	Wrote a monograph titled, *"Effectiveness and Efficiency: Random Reflections on Health Services"* (1972) Father of Evidence-Based Medicine (EBM) Father of modern clinical epidemiology First President of the Faculty of Community Medicine (Pubic Health) of the Royal College of Physicians in the UK (1972–1975) Promulgated randomised clinical trials (RCTs) Broadly proposed the following themes, namely, epidemiological research, critical thinking and controlled clinical trials, health services assessment/ research, systematic reviews, and humanist care

Thomas C. Chalmers (1917, New York City, US—1995, New Hampshire, US)	Associate Director for Clinical Care and Director of the Clinical Center at the National Institutes of Health (NIH) in Bethesda, Maryland President, Mount Sinai Medical Center, New York Dean, Mount Sinai medical school, New York Harvard School of Public Health, Boston, MA MetaWorks	A pioneer of RCTs and systematic reviews (champion of RCTs) "The acknowledged leader in the design, conduct and evaluation of clinical trials" [as quoted by New York Academy of Medicine] *Notable publications:* Chalmers TC. Randomize the first patient! N Engl J Med 1977;296:107. https://doi.org/10.1056/NEJM197701132960214 Chalmers TC, Matta RJ, Smith H Jr., Kunzler AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. N Engl J Med 1977;297:1091–1096. https://doi.org/10.1056/NEJM197711172972004 [one of the first meta-analyses in clinical sciences textbooks are often seriously inconsistent with existing evidence, according to cumulative meta-analyses] Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992;327:248–254. https://doi.org/10.1056/NEJM199207233270406 Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. JAMA 1992;268:240–248 [a landmark paper that showed authoritative medical evidence for management of MI] Started the "Department of Geriatrics" in Mount Sinai Medical School in New York City [which was one of the first of its kind at an American medical school] Forerunner who sought for clinical trial registries ("better method of centrally recording the sporadic individual trials now going on") Proposer of the checklist for assessment of trial quality (even before the now established CONSORT checklist) [A proposal for structured reporting of randomized controlled trials. The Standards of Reporting Trials Group. JAMA 1994;272:1926–1931] "Thomas C. Chalmers prize student scholarship program" established by the Society for Clinical Trials (SCT) "Thomas C. Chalmers prize" awarded each year by the Cochrane collaboration for addressing methodological issues related to systematic reviews given to lead early career investigators (authors)

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Table 4.1 (continued)

Name	Notable Affiliation(s)	Contributions and Accolades
Alvan R. Feinstein (1925, Philadelphia, Pennsylvania, US—2001, Toronto, Ontario, Canada)	Medical Director at Irvington House Professor of Medicine and Epidemiology at Yale University School of Medicine Founding Director and Director (emeritus), Robert Wood Johnson Clinical Scholars Program at Yale	Father of modern clinical epidemiology Founder of clinical epidemiology Founder and editor of the *Journal of Clinical Epidemiology* Coined the words, 'comorbidity' [1970], 'trohoc' (cohort spelled backwards) [1973], and many others Bestowed with the following awards *Francis Gilman Blake award* as outstanding teacher to Yale medical students (1969) *Richard and Hinda Rosenthal Foundation Award* from the American College of Physicians (1982) *Robert J. Glaser Annual Award* from the Society for General Internal Medicine (1987) *J. Allyn Taylor International Prize* in Medicine (1987) *Gairdner Foundation (Canada) International Award* (1993) *"Sterling Professor of Medicine and Epidemiology"*, Yale University (1991) *"Distinguished teacher award"* by the American College of Physicians in 1998 *Oscar B. Hunter Award* from the American Society for Clinical Pharmacology and Therapeutics (1999) *Notable books:* "Clinical Judgment" (©1967): *Described the goals and methods of clinical reasoning* "Clinical Biostatistics" (©1977): *Presented the structure and contents of clinical research with groups* "Clinical Epidemiology: The architecture of clinical research" (©1985): *Described the strategies used to form clinical indexes and rating scales for important clinical phenomena such as pain, distress and disability* "Clinimetrics" (ISBN 978–0300038064) (©1987) "Multivariable analysis" (ISBN 978–0300062991) (©1996) "Principles of Medical Statistics" (ISBN 9781032477947) (©2002) Alvan R. Feinstein memorial award *(the award is to be given to an American physician who has made a major contribution to the science of patient care in activities that Dr. Feinstein has broadly defined as clinical epidemiology or clinimetrics, involving the direct study of patients' clinical conditions. This award is given every other year.)*

Name	Notable Affiliation(s)	Contributions and Accolades
David L. Sackett (1934, Chicago—2015, Canada)	Director, Trout Research and Education Centre at Irish Lake, Markdale, Ontario, Canada Founding Chair, Clinical Epidemiology and Biostatistics, McMaster University Chief Teaching Fellow, Harvard School of Public Health Physician-in-Chief, Medicine, Chedoke-McMaster Hospitals	Champion of EBM Father of EBM Organized a series of Health Care Evaluation Seminars at most of the Canadian Health Science Centres (1970s) Developed cost-utility analysis (1972) [along with Torrance GW, and Thomas WH] Initiated the journal titled, *"Evidence-Based Medicine"* (1995) [along with Davidoff F, Haynes B, and Smith R] [currently known as the *"BMJ evidence-based medicine (BMJ EBM)"*] Founding Director (1994) of the Centre for Evidence-Based Medicine (CEBM), Nuffield Department of Primary Care Health Sciences, University of Oxford First chair of the Cochrane Collaboration (foundation chair of the Cochrane Collaboration Steering Group) Inducted into the Canadian Medical Hall of Fame (2000) Appointed Officer of the Order of Canada (2001) Awarded Canada Gairdner Foundation Wightman Award (2009) *Notable publications:* Sackett DL. Bias in analytic research. J Chronic Dis 1979;32:51–63. https://doi.org/10.1016/0021-9681(79)90012-2 Sackett D. How to read clinical journals: I. Why to read them and how to start reading them critically. Can Med Assoc J 1981;124:555–558 Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1986;89:2S–3S Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318:1728–1733. https://doi.org/10.1056/NEJM198806303182605 *[the concept "number needed to treat" was introduced]* Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71–72. https://doi.org/10.1136/bmj.312.7023.71 Wrote a book titled, *"Clinical Epidemiology: A Basic Science for Clinical Medicine"* (1985) [along with Haynes RB and Tugwell P.] Book: *Evidence Based Medicine: How to Practice and Teach EBM* (1997) {"the bible of evidence-based medicine"}

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Table 4.1 (continued)

Name	Notable Affiliation(s)	Contributions and Accolades
Walter Spitzer (1937, Asuncion, Paraguay –2006)	Emeritus Professor of Epidemiology at McGill University Assistant and then as Associate Professor of Clinical Epidemiology and Biostatistics at McMaster University	Founding Co-Editor (along with Feinstein) and Editor Emeritus of the *Journal of Clinical Epidemiology* Founder of the Kellogg Centre for Advanced Studies in Primary Care, McGill University Introduced one of the first instruments for measuring the 'quality of life'. Established an Institute of Pharmacoepidemiology and Technology Assessment. Leader of the Canadian Task Force on the Periodic Health Examination which introduced grading of evidence to back up each recommendation and "Grade A" was only assigned if the recommendation was based on evidence from randomized trials. *Notable publications:* Spitzer WO, Sackett DL, Sibley JC, et al. The Burlington randomized trial of the nurse practitioner. N Engl J Med 1974;290:251–256. Spitzer WO, Feinstein AR, Sackett DL. What is a health care trial? JAMA 1975;233:161–163. Ibrahim MA, Spitzer WO. The case control study: the problem and the prospect. J Chronic Dis 1979;32:139–144. Spitzer WO, Kergin DJ, Yoshida MA, Russell WA, Hackett BC, Goldsmith CH. Nurse practitioners in primary care. 3. The southern Ontario randomized trial. Can Med Assoc J 1973;108:1005–1016
Sir Iain Chalmers (b. 1943, Liverpool, Lancashire, England)	Worked for United Nations in a Palestinian refugee camp (UN Relief and Works Agency) in the Gaza Strip (1969–1970) Coordinating editor, the James Lind library (https://www.jameslindlibrary.org/) and testing treatments interactive (https://en.testingtreatments.org/), Oxford, UK Articles editor, Centre for Evidence-Based Medicine, University of Oxford, UK British health services researcher	Performed the first systematic review (meta-analysis) of RCTs (1976) Created the National Perinatal Epidemiology Unit at Oxford University (1978) [funded by the World Health Organization and the UK Department of Health] Wrote the two-volume book titled, *"Effective Care in Pregnancy and Childbirth"* (1989) *(widely recognized as being the first evidence-based text book in any medical specialty)* Founding Director of the National Perinatal Epidemiology Unit (NPEU), Oxford (1978) First Director of the UK Cochrane Centre (1992) Co-founder of the Cochrane collaboration Sobriquets: "Maverick master of medical evidence", "systematic review man" Lifetime Achievement Award 2014 (BMJ) Knighted for services to healthcare [Knight Bachelor] (2000) C.-E. A. Winslow Award by Yale School of Public Health (2010) *Notable publications:* Chalmers I, Dickersin K, Chalmers TC. Getting to grips with Archie Cochrane's agenda. BMJ 1992;305:786–788. https://doi.org/10.1136/bmj.305.6857.786 Chalmers I. The Cochrane collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. Ann N Y Acad Sci 1993;703:156–165. https://doi.org/10.1111/j.1749-6632.1993.tb26345.x Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical Evidence of Bias: Dimensions of Methodological Quality Associated With Estimates of Treatment Effects in Controlled Trials. *JAMA* 1995;273:408–412. https://doi.org/10.1001/jama.1995.03520290060030 Chalmers I, Bracken MB, Djulbegovic B, et al. How to increase value and reduce waste when research priorities are set. Lancet 2014;383:156–165. https://doi.org/10.1016/S0140-6736(13)62229-1

Peter Tugwell (b. 1944, Egypt)	Senior Scientist, Methodological & Implementation Research, Ottawa Hospital Research Institute Director, Centre for Global Health, University of Ottawa Co-Director, WHO Collaborating Centre for Knowledge Translation and Health Technology Assessment in Health Equity, Bruyere Research Institute Professor, Medicine and Epidemiology & Community Medicine, University of Ottawa Chair, Management Group member, OMERACT® - Outcome Measures in Rheumatology	One of the founders of EBM and founding member of Cochrane Founding Director of the International Clinical Epidemiology Network (INCLEN) Training Centre at McMaster University Co-Editor-in-Chief, *Journal of Clinical Epidemiology* (2001–2022) Supported in the development of the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses Fellow of the Canadian Academy of Health Sciences Officer of the Order of Canada (2013) Canadian Institutes of Health Research (CIHR) Barer-Flood Prize (2020) *Notable publications*: Tugwell P, Boers M, Simon L, Strand V, Wells G, Shea B, Brooks P. Evidence-based rheumatology. London: BMJ books, 2005 Sackett,D. L. and Haynes,R. B. and Tugwell,P., 19,862,027,657, English, Book, USA, 9780316765954, Boston, Clinical epidemiology: a basic science for clinical medicine., (xiii +370 pp.), Little, Brown and Company, Clinical epidemiology: a basic science for clinical medicine., (1985)

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Table 4.1 (continued)

Name	Notable Affiliation(s)	Contributions and Accolades
Sir Muir Gray (b. 1944?)	Executive Director, Oxford Value and Stewardship Programme Director, the Optimal Ageing Programme Director, Research and Development for Anglia and Oxford Regional Health Authority Director, UK National Screening Committee Director, Clinical Knowledge, Process, and Safety for the National Health Service (NHS) Director, National Knowledge Service Chief Knowledge Officer, NHS Visiting Professor, Nuffield Department of Surgical Sciences, University of Oxford Chair, NHS Social Care Digital Service Contractor, Public Health England	Establishment of the Cochrane Collaboration Founding Director, Critical Appraisal Skills Programme (CASP) Founder, National Library for health Founder, Centre for Sustainable Healthcare Co-director, Department of Health's Quality Innovation Productivity and Prevention (QIPP) Right Care Programme, NHS Founder Director, Better Value Healthcare Founder, Oxford Centre for Triple Value Healthcare Knighted in 2005 for the development of the foetal, maternal and child screening programme and the creation of the National Library for health CBE (2000) *Notable publications:* Gray M, Jani A. Money isn't the most critical resource-we need to consider time and carbon. BMJ. 2022;379:o3002. https://doi.org/10.1136/bmj.o3002 Gray M, Jani A, Collins A. Reduce waste in the NHS to deliver population health. BMJ. 2024;385:q949. https://doi.org/10.1136/bmj.q949 Gray M, Meakins JL. Evidence-based surgical practice and patient-centered care: Inevitable. Surg Clin North Am. 2006;86:217–220. https://doi.org/10.1016/j.suc.2005.11.005 Book: Sod seventy!: The guide to living well, © 2017 Book: Sod sitting, get moving!: Getting active in your 60s, 70s and beyond Book: Sod sixty!: The guide to living well Book: Sod it! Eat well: Healthy eating in your 60s, 70s and beyond

Drummond Rennie (b. 1945?)	Former Contributing Deputy Editor, JAMA Adjunct Professor of Medicine, P.R. Lee Institute for Health Policy Studies, University of California, San Francisco Editor, NEJM	Founder and Director Emeritus, Peer Review Congress (directed seven congresses on peer review in biomedical publication) Editor, JAMAevidence Co-Director, San Francisco Cochrane Center Member, Commission on Research Integrity to the Public Health Service President, World Association of Medical Editors Award for Scientific Freedom and Responsibility [by the American Association for the Advancement of Science (AAAS) in 2008] *Notable publications:* Book titled, *"The Rational Clinical Examination: Evidence-Based Clinical Diagnosis"* published by the American Medical Association (2009) Rennie D. Guarding the guardians: a conference on editorial peer review. JAMA 1986;256:2391–2392. Rennie D, Yank V, Emanuel L. When authorship fails: a proposal to make contributors accountable. JAMA 1997;278: 579–85. Rennie D. The present state of medical journals. Lancet 1998;352 Suppl 2:SII18-SII22. https://doi.org/10.1016/s0140-6736(98)90295-1 Rennie D. CONSORT revised—improving the reporting of randomized trials. JAMA 2001;285: 2006–7. Rennie D. Integrity in scientific publishing. Health Serv Res 2010;45:885–896. https://doi.org/10.1111/j.1475-6773.2010.01088.x Rennie D. Let's make peer review scientific. Nature. 2016;535(7610):31–33. https://doi.org/10.1038/535031a

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Table 4.1 (continued)

Name	Notable Affiliation(s)	Contributions and Accolades
Brian Haynes (b. 1945?)	Professor of Clinical Epidemiology and Biostatistics and Professor of Medicine, Faculty of Health Sciences, McMaster University Chief of the Health Information Research Unit (HiRU), McMaster University Professor Emeritus, Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University	Founding Editor of ACP Journal Club Former Director, CEBM Director of the Canadian Cochrane Centre One of the founders of EBM Officer of Order of Canada (OC) Rosenthal Award of the American College of Physicians *Notable publications:* Haynes RB. Where's the meat in clinical journals? ACP Journal Club 1993;119: A22-A23 Haynes RB, Cotoi C, Holland J, et al. Second-order peer review of the medical literature for clinical practitioners. JAMA 2006;295:1801–1808. https://doi.org/10.1001/jama.295.15.1801 Book: Clinical epidemiology: A basic science for clinical medicine Book: Evidence-based medicine: How to practice and teach—Fifth edition (2018)

Peter C. Gøtzsche (b. 1949, Næstved, Denmark)	Head, Nordic Cochrane Centre Professor, Clinical Research Review and Design, University of Copenhagen Visiting Professor, Institute of Health and Society, Newcastle University	Founder, Institute for Scientific Freedom (2019) Co-founder of the Cochrane collaboration *Notable publications:* Gøtzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable?. Lancet 2000;355:129–134. https://doi.org/10.1016/S0140-6736(99)06065-1 Gotzsche PC. Why we need a broad perspective on meta-analysis. It may be crucially important for patients. BMJ 2000;321(7261):585–586. https://doi.org/10.1136/bmj.321.7261.585 Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med 2004;256:91–100. https://doi.org/10.1111/j.1365-2796.2004.01355.x Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane database Syst rev. 2010;2010:CD003974. https://doi.org/10.1002/14651858.CD003974.pub3 Gøtzsche PC, Kassirer JP, Woolley KL, et al. What should be done to tackle ghostwriting in the medical literature?. PLoS Med 2009;6:e23. https://doi.org/10.1371/journal.pmed.1000023 Book: Deadly medicines and organised crime: How big pharma has corrupted healthcare, CRC Press, © 2013 *[Winner, British Medical Association Annual Book Award, Basics of Medicine, 2014]* Book: Vaccines: Truth, lies, and controversy (2020) Book: Mammography Screening: Truth, Lies, and Controversy (2012) *[Winner, Prescrire Prize 2012]* Book: Survival in an overmedicated world: Look up the evidence yourself (2019) Book: Death of a whistleblower and Cochrane's moral collapse (2019) Book: Deadly psychiatry and organized denial (2015) Book: Rational Diagnosis and Treatment: Evidence-Based Clinical Decision-Making (2007)

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Table 4.1 (continued)

Name	Notable Affiliation(s)	Contributions and Accolades
Kay Dickersin (b. 1951, Philadelphia, Pennsylvania, US)	Professor Emeritus, Epidemiology, Johns Hopkins Bloomberg School of Public Health Director, Center for Clinical Trials and Evidence Synthesis, Johns Hopkins Bloomberg School of Public Health Center for Drug Safety and Effectiveness Director, Cochrane eyes and vision review group, US satellite (CEVG@US)	Founder, National Breast Cancer Coalition (NBCC) (1991) Founder, International Clinical Trials Registry Platform (ICTRP) [WHO] Director, US Cochrane Center (USCC) Development of Cochrane's Central Register of Controlled Trials (CENTRAL) Founder, Consumers United for evidence-based healthcare (CUE) Awards and Honours Women's Hall of Fame, Baltimore City Commission for Women (1996) "Maryland's Top 100 Women," Daily Record (2006) MAMM magazine's "50 who made a difference." (1998) "Exceptional advocate," National Breast Cancer Coalition. (2000) "Contributions and enduring commitment to the eradication of cancer," American Association for Cancer Research. (2007) Ingram Olkin award, from the Society for Research Synthesis Methods for lifetime contributions to the field (2014) *Notable publications:* Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H Jr. Publication bias and clinical trials. Control Clin Trials 1987;8:343–353. https://doi.org/10.1016/0197-2456(87)90155-3 Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA. 1990;263(10):1385–1389. https://doi.org/10.1001/jama.1990.03440100097014 Dickersin K, Berlin JA. Meta-analysis: State-of-the-science. Epidemiol rev. 1992;14:154–176. https://doi.org/10.1093/oxfordjournals.epirev.a036084 Dickersin K, Rennie D. Registering Clinical Trials. JAMA 2003;290:516–523. https://doi.org/10.1001/jama.290.4.516 Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012;367:1355–1360. https://doi.org/10.1056/NEJMsr1203730 Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med 2009;361:1963–71. Dickersin K. To reform U.S. health care, start with systematic reviews. Science 2010;329:516–7. Dickersin K, Straus SE, Bero LA. Evidence based medicine: increasing, not dictating, choice. BMJ 2007;334:s10. https://doi.org/10.1136/bmj.39062.639444.94

Gordon Guyatt (b. 1953, Hamilton, Ontario, Canada)	Distinguished Professor in the Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University Professor, Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University Director of the Internal Medicine Residence Program Medical Reform Group, the Canadian health care system Member, Michael G. DeGroote Cochrane Canada Centre at McMaster, Faculty of Health Sciences Member, Centre for Medicinal Cannabis Research (CMCR), Faculty of Health Sciences	Coined the term "Evidence-based medicine" (1991) One of the most-cited living scientists in the world (Google scholar: 607058 citations, h-index = 304) Spearheaded the formation of the Evidence Based Medicine Working Group Played a key role in the development of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, now adopted by more than 90 organizations worldwide Awards and Honours 2024: Henry G. Friesen International Prize in Health Research 2022: Einstein Foundation Award for promoting quality in research 2022: Honorary Doctorate at the Faculty of Medicine of the University of Helsinki, Helsinki, Finland 2016: Inducted into the Canadian Medical Hall of Fame 2013: CIHR researcher of the year 2012: Fellow of the Royal Society of Canada 2012: The Queen Elizabeth II Diamond Jubilee Medal 2011: Officer of the Order of Canada 2011: Fellow of the Canadian Academy of Health Sciences 2009: Jack Hirsh Award for outstanding academic achievement 1996: McMaster University President's award for excellence in teaching *Notable publications:* Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992;268:2420–2425. https://doi.org/10.1001/jama.1992.03490170092032 Guyatt GH, Rennie D. Users' Guides to the Medical Literature. JAMA 1993;270:2096–2097. https://doi.org/10.1001/jama.1993.03510170086037 Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995;274:1800–1804. https://doi.org/10.1001/jama.274.22.1800 Grading quality of evidence and strength of recommendations. BMJ 2004; 328: 1490. https://doi.org/10.1136/bmj.328.7454.1490 Guyatt G H, Oxman A D, Vist G E, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924. https://doi.org/10.1136/bmj.39489.470347.AD Moher D, Liberati A, Tetzlaff J, Altman D G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement BMJ 2009; 339: b2535. https://doi.org/10.1136/bmj.b2535 Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332. https://doi.org/10.1136/bmj.c332 Users' guides to the medical literature: A manual for evidence-based clinical practice, third ed., 2014, Gordon Guyatt, Drummond Rennie, Maureen O. Meade, Deborah J. Cook

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Table 4.1 (continued)

Name	Notable Affiliation(s)	Contributions and Accolades
Paul Glasziou (b. 1954)	Director, Centre for Evidence-Based Medicine, Oxford (2003–2010) Director and Professor, Evidence-Based Practice, Bond University Director, Institute for Evidence Based Healthcare, Bond University Director, Faculty of Health Sciences & Medicine, Bond University	Chair, Handbook of Non-Drug Interventions (HANDI) [RACGP - the Royal Australian College of General Practitioners] (online formulary of non-drug interventions in healthcare) Founder, Systematic Review Accelerator (SRA) project, Bond University Co-founder, International Collaboration for the Automation of Systematic Reviews (ICASR) Fellow of the Australian Academy of Health and Medical Sciences (2015) Officer of the Order of Australia (2021) *Notable publications:* Book: Systematic reviews in health care: A practical guide Book: Decision making in health care and medicine: Integrating evidence and values Book: An evidence-based medicine workbook Book: Clinical thinking: Evidence, communication and decision-making Book: Evidence-based medicine: How to practice and teach EBM Book: Evidence-based medical monitoring: Principles and practice Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet 2009;374:86–89. https://doi.org/10.1016/S0140-6736(09)60329-9 Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up?. PLoS Med 2010;7:e1000326. https://doi.org/10.1371/journal.pmed.1000326 Lane R. Paul Glasziou: surfing the wave of evidence-based medicine. Lancet 2014;383:209. https://doi.org/10.1016/S0140-6736(13)62386-7 Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687. https://doi.org/10.1136/bmj.g1687 Glasziou P, Chalmers I. Research waste is still a scandal—an essay by Paul Glasziou and Iain Chalmers BMJ 2018; 363:k4645

John P.A. Ioannidis (b. 1965, New York City)	Co-director, Meta-Research Innovation Center at Stanford (METRICS) Professor of medicine, Stanford prevention research center Professor, epidemiology and population health Director/ C.F. Rehnborg chair at Stanford prevention research center Chair, Department of Hygiene and Epidemiology, University of Ioannina Medical School (1999–2010) Adjunct professor positions at Harvard, tufts, and Imperial college	One of the most cited scientists in history. *The Atlantic* magazine (2010): “One of the most influential scientists alive.” Referred to as “the conscience of science” A meta-research enthusiast (meta-research: “Research on research” or “the science of science”) Highly cited researcher (Clarivate) in clinical medicine, social sciences and psychiatry/psychology. h-index = 268 (Google scholar), current citation rate: 6000 new citations per month (among the 6 scientists worldwide who are currently the most commonly cited). *[“when contrasted against my vast ignorance, these values offer excellent proof that citation metrics can be horribly unreliable.”—As stated by Ioannidis himself]* President, Association of American Physicians (2023–24) President, Society for Research Synthesis Methodology Editorial board, Journal of the American Medical Association (JAMA), Journal of the National Cancer Institute (JNCI), PLoS, and the Lancet. Editor-in-Chief, European Journal of Clinical Investigation (2010–2019) *Awards and honors:* European Award for Excellence in Clinical Science (2007) Chanchlani Global Health Award (2017) Epiphany Science Courage Award (2018) Einstein fellow (2018) Gordon award (2019) Albert Stuyvenberg Medal (2021) Harwood Prize (2022) Founders’ medal for lifetime contributions to meta-science (2024). *Notable publications:* Ioannidis JP, Lau J. On meta-analyses of meta-analyses. Lancet 1996;348:756. https://doi.org/10.1016/S0140-6736(05)65647-4 Ioannidis JP. Why most published research findings are false. PLoS Med 2005;2:e124. https://doi.org/10.1371/journal.pmed.0020124 *[most-accessed article in the history of public library of science (>three million hits)]* Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. JAMA 2005;294:218–228. https://doi.org/10.1001/jama.294.2.218 Ioannidis JP. Evidence-based medicine has been hijacked: a report to David Sackett. J Clin Epidemiol 2016;73:82–86. https://doi.org/10.1016/j.jclinepi.2016.02.012

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Table 4.1 (continued)

Name	Notable Affiliation(s)	Contributions and Accolades
		Goodman SN, Fanelli D, Ioannidis JP. What does research reproducibility mean? Sci Transl Med 2016;8:341 ps12. https://doi.org/10.1126/scitranslmed.aaf5027 Ioannidis JPA. Meta-research: Why research on research matters. PLoS Biol 2018;16:e2005468. https://doi.org/10.1371/journal.pbio.2005468 Literary Books (in Greek): "Toccata for the Girl with the Burnt Face" (Kedros 2012) and "Variations on the Art of the Fugue and a Desperate Ricercar" (Kedros 2014) Ioannidis JPA, Baas J, Klavans R, Boyack KW. A standardized citation metrics author database annotated for scientific field. PLoS Biol 2019;17:e3000384. https://doi.org/10.1371/journal.pbio.3000384 *[World's top 2% scientists]* Ioannidis JPA. The end of the COVID-19 pandemic. Eur J Clin Invest 2022;52:e13782. https://doi.org/10.1111/eci.13782 Ioannidis JPA, Pezzullo AM, Boccia S. The Rapid Growth of Mega-Journals: Threats and Opportunities. JAMA 2023;329:1253–1254. https://doi.org/10.1001/jama.2023.3212 Ioannidis JP. Transparency, bias, and reproducibility across science: a meta-research view. J Clin Invest 2024;134:e181923. https://doi.org/10.1172/JCI181923

Richard Smith (b. 1968, UK)	Former Editor-in-Chief, BMJ (1991–2004) Director, UnitedHealth Chronic Disease Initiative Board of Directors, Public Library of Science Honorary Professor, Imperial College London and the University of Warwick Chair, UK Health Alliance on Climate Change	Chief Executive, BMJ Publishing Group Chair, Cochrane Library Oversight Committee Member, UK Panel on Research Integrity Founding Fellow, Academy of Medical Sciences Chairman, the Point of Care Foundation Chair, Lancet Commission on the Value of Death Chairman of the Board of Directors, Patients Know Best *(a company that gives patients access to and control over all their health and social care data, including all records and test results)* Chair, icddr,b (International Centre for Diarrhoeal Disease, Bangladesh) *Notable publications*: Richard Smith: Dying of cancer is the best death (31 December 2014) BMJ Blog Richard Smith: Medical research—still a scandal (31 January 2014) BMJ Blog Richard Smith: How medicine is destroying itself (19 February 2018) BMJ Blog Richard Smith: Is cancer still the best way to die? (4 December 2020) BMJ Blog Davidoff F, Haynes B, Sackett D, Smith R. Evidence based medicine. BMJ 1995;310:1085–1086. https://doi.org/10.1136/bmj.310.6987.1085 Smith R. What clinical information do doctors need? BMJ 1996;313:1062–1068. https://doi.org/10.1136/bmj.313.7064.1062 Smith R. Medical journals are an extension of the marketing arm of pharmaceutical companies. PLoS Med 2005;2:e138. https://doi.org/10.1371/journal.pmed.0020138 Smith R. Peer review: a flawed process at the heart of science and journals. J R Soc Med 2006;99:178–182. https://doi.org/10.1177/014107680609900414 Smith R. The trouble with medical journals. J R Soc Med 2006;99:115–119. https://doi.org/10.1177/014107680609900311 Sallnow L, Smith R, Ahmedzai SH, et al. Report of the Lancet Commission on the Value of Death: bringing death back into life. Lancet 2022;399:837–884. https://doi.org/10.1016/S0140-6736(21)02314-X

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Table 4.1 (continued)

Name	Notable Affiliation(s)	Contributions and Accolades
Carl Heneghan (b. 1968, UK)	Professor of Evidence-Based Medicine and Director, Centre for Evidence-Based Medicine (CEBM), Oxford Co-Director, Global Centre for Healthcare and Urbanisation (GCHU), Kellogg college	Among the top 1% most cited scientists in his field Over 450 peer-reviewed publications (current h-index 99) and published over 110 systematic reviews Former Editor-in-Chief of BMJ Evidence-Based Medicine Founder of the "AllTrials campaign" (https://senseaboutscience.org/alltrials/) Writes regularly at Trust the Evidence (https://trusttheevidence.substack.com/)

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