1 The Importance of Applying Evidence-Based Medicine in Clinical Practice

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What Is Evidence-Based Medicine?

The first scientific origins of evidence-based medicine (EBM) can be traced back to mid-nineteenth century in the works of John Snow and Pierre Charles Alexandre Louis [1], or even earlier in James Lind's study on scurvy [2]. Despite these innovative attempts, clinical practice in medicine was still largely based on expert opinion, driven by physiological rationale and individual clinician's expertise. It was not until mid-twentieth century that the medical community began to realize that reliance on uncontrolled clinical experience and pathophysiological reasoning alone, was flawed [3]. In fact, in 1962 the Food and Drug Administration passed the Kefauver-Harris Amendment in the United States, which required evidence from rigorous clinical trials in order to determine drug efficacy [4]. Later, in the 1970s and 1980s, the seminal works of Archie Cochrane [5], David Eddy [6] and David Sackett [7] further highlighted the need for strengthening the empirical practice of medicine and established the key concepts behind evidence-based practice.

The first published use of the term "evidence-based" in medical literature appeared in a series of articles by D. Eddy in 1990 [8]. These papers discussed the limitations of expert opinion in medical decision making, but focused mainly on the development of clinical guidelines, arguing that these should be based on substantial evidence, rather than subjective judgment or consensus. In 1991, G.H. Guyatt introduced the term "evidence-based medicine", which differed from the definition proposed by D. Eddy, as it had a more clinical orientation, promoting the careful assessment of existing research evidence by physicians and its application in their daily decisions about individual patients [9]. A more comprehensive article, published a year later by the EBM Working Group, presented EBM as a novel paradigm in the teaching and practice of medicine [10], while the User's Guides to the Medical Literature series in JAMA brought the underlying concepts of EBM to the attention of a wider medical community [11]. Subsequently, the influence of EBM has been constantly growing worldwide, resulting in its recognition as one of the most important medical milestones since 1840 [12].

The Principles of Evidence-Based Medicine

In its most commonly cited definition, EBM is described as "the conscientious, explicit, and

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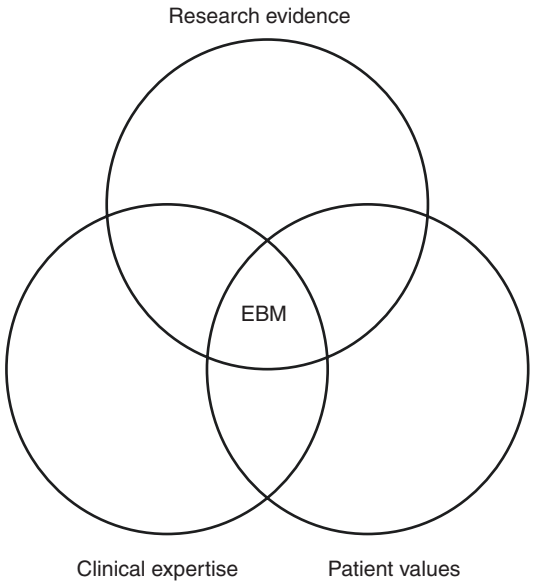

Fig. 1.1 The key principles of evidence-based medicine (EBM)

judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research" [13]. Later, this definition was refined, emphasizing the importance of patients' values and preferences in optimal clinical decision making. As a result, EBM can more accurately be described as the "integration of best research evidence with clinical expertise and patient values" [14], as depicted in Fig. 1.1. A variation of this characterization has also incorporated the clinical state and circumstances within the context of clinical expertise [15], while in a broader definition, that of evidence-based practice, health care resources are also considered an important parameter for optimal decision making [16]. Regardless of the exact definition used, the principles of EBM emphasize that all medical decisions about a therapeutic or diagnostic procedure should be based on high quality, up-to-date research evidence, acknowledge the importance of clinical expertise and intuition and highlight that patient value and preference judgements are implicit in every clinical decision.

Best Research Evidence

Research evidence originates from various types of studies, including laboratory observations, pathophysiologic studies, case reports, observational studies, or more advanced applied clinical research from randomized controlled trials (RCTs). EBM acknowledges that not all research is created equal and that some study designs are more suitable than others in answering specific research questions [1]. Therefore, EBM, from its early inception, has suggested a hierarchy for ranking the quality of evidence [17]. Figure 1.2 illustrates such a hierarchy framework of evidence. The pyramid shape is used to represent the decrease in risk of bias (or increase in quality) associated with each study type as one goes up the pyramid.

In this hierarchy, RCTs are placed at the highest level of the pyramid, thus represent the most reliable evidence for determining the effectiveness of medical interventions, as opposed to observational studies or other study designs. Notably, since the first documented report of an RCT in 1948 (streptomycin treatment for pulmonary tuberculosis [18]), the RCT has been considered as the most scientifically rigorous method for hypothesis testing [19]. In a typical RCT, participants are randomly allocated to one or another intervention and are followed for a specific period. At the end of the study, any differences observed in predefined outcomes are attributed solely to the trial intervention [19].

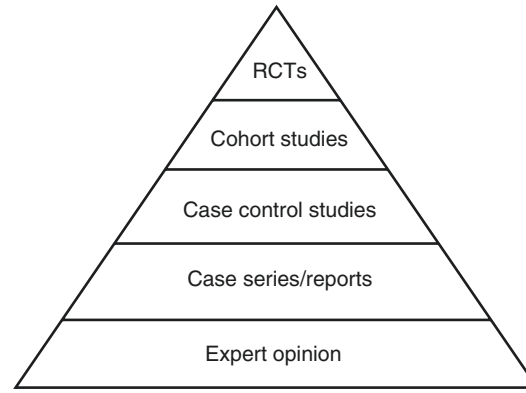

Fig. 1.2 The evidence-based medicine pyramid

However, it is now recognized that evidence from RCTs is not necessarily always of high quality and that not all research questions can be answered through an RCT [1]. For example, the diagnostic accuracy of a medical test can be answered from a well-conducted cross-sectional study, while an observational study is required for a question about prognosis [13]. On this account, a revised form of the traditional evidence pyramid has been proposed, in which the straight lines separating study types have been converted to wavy lines, suggesting that there is overlap in study quality among different designs [20]. For instance, it is possible that for a specific research question observational studies provide more reliable information than RCTs. Furthermore, quality of evidence does not depend solely on study type, but on other parameters as well, such as bias in study implementation, imprecision, inconsistency and indirectness. As a result, a more sophisticated approach to rating evidence quality has been developed, termed the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system [21]. In the GRADE framework, non-RCTs begin as low-quality evidence, but can be rated up based on the parameters mentioned above, as opposed to RCTs, that start at high level and can be rated down.

Systematic reviews and meta-analyses are an additional important tool of EBM [22]. A systematic review provides a summary of all primary studies about a specific clinical question, using predefined methods for identifying, critically appraising and synthesizing all available research evidence. Due to their explicit methodology and cumulative data synthesis, systematic reviews are considered to provide more reliable and accurate conclusions compared to individual studies [22].

Clinical Expertise

The practice of EBM dictates that research evidence alone is inadequate for optimal decision making if the information is not efficiently combined with clinical expertise. Clinical expertise includes the general basic skills and proficiency acquired through clinical practice, as well as the experience of the individual practitioner [23]. Clinical expertise can be reflected in many ways, including obtaining the right diagnosis, determining relevant treatment options and placing research evidence within the context of the individual patient's clinical state and circumstances [23, 24].

Obtaining a history and conducting a physical examination are essential skills for getting the right diagnosis, that come only from thorough background training and clinical experience [24]. In addition, many diagnostic tests may differ in their accuracy depending on the skill of the practitioner [10]. In a similar manner, the effectiveness and complications associated with therapeutic interventions, particularly surgical interventions, can also depend on individual clinician's experience and skills [10]. Finally, after obtaining the best relevant research evidence, the clinician, using sound clinical judgement, must determine whether the external evidence can be applied to the individual patient. In doing so, the clinician must consider all relevant comorbidities that may influence the treatment effect, in addition to research-related factors, such as whether the available studies have measured all important outcomes, included relevant comparators and have a reasonable follow up period [24, 25]. Additional features of clinical expertise are related to the ability to provide patients with the information they need in a manner that facilitates informed decision making and developing values such as integrity, compassion, respect and sustained professional curiosity [15, 26].

A concise definition summarizing all the essential characteristics that constitute clinical expertise, has been given by W.S. Richardson: "Clinical expertise includes the deliberate practice of communication skills, clinical skills, and decision skills, as well as the experiential learning that comes through the care of sick persons, with the development of clinical judgment" [26].

Patient Values and Preferences

Clinical expertise and knowing the best research evidence are necessary, but insufficient for delivering the highest quality of care. The third key principle of EBM advocates that clinical decisions and recommendations must attend to the values and preferences of the informed patient. This patient centered approach means that it is not the clinician who should exclusively decide what will happen to the patient, but it is also the patient's right to participate in decision making about their treatment options or diagnostic procedures [27].

Values and preferences refer to patient characteristics that can variably affect decision making during the clinical encounter. These may include experience of former and current illnesses or other relevant life experiences, health habits, goals and expectations, social or family support, and personal beliefs about medical interventions [26]. Depending on these factors, patients may have either no views or unchangeable views on how to proceed with their treatment or diagnostic options. Of note, research has shown that considerable variation exists between physicians' and patients' preferences when it comes to weighting the benefits and drawbacks of therapeutic options [28]. Moreover, patients' actions may differ not only from their clinician's advice, but also from the preferences and views they expressed during the clinical consultation [15]. Thus, in addition to exploring patients' perceptions and values, a clinician should ideally be able to understand the procedures individuals use to consider their treatment options, in order to assess whether patients are likely to adhere to their prescriptions and therapeutic recommendations [29, 30].

From an ethical point of view, respecting patients' preferences should be justified on moral grounds alone [31]. Patient centered care has a theoretical foundation in the principle of patient autonomy, a belief that originates from the patients' rights movement in the 1960s [32]. Since then, several medical associations, institutions and health planners have endorsed and incorporated patient centered care in their guidelines, recommendations and policies. In fact, the National Health Service Constitution in the United Kingdom advocates patient participation in decision making [33], while in the United States, the Institute of Medicine, in its "Quality Chasm" report, has designated evidence-based patient centered care as one of six key elements of high quality care [34].

Applying Evidence-Based Medicine in Clinical Practice

The practice of EBM involves a multi-stage process [35]. First, the clinical problem must be translated into an answerable question. Subsequently, one needs to retrieve the best evidence that answers this question and critically appraise the findings with respect to their validity and usefulness. The fourth step involves implementing the results of the appraisal into clinical practice, while the final step is related to evaluating the effectiveness and efficiency in executing previous steps and seeking ways to improve them [35].

It has been suggested that clinicians can incorporate this five-step process into their practices in three different ways [35]. First, in the "doing" mode, at least the four first steps are followed before a medical decision is made. In the "using" mode, step 3 is skipped by restricting the search to evidence that has already undergone critical appraisal, such as databases of guidelines or pre-appraised information. Finally, in the "replicating" mode, decisions are based on respected leaders' opinion, thus both steps 2 and 3 are omitted. Ideally, the "doing" mode should be followed in most cases, however depending on the specific clinical problem they encounter, physicians can move back and forth between the three modes [35].

Formulating an Answerable Question

The practice of EBM should begin with a well formulated clinical question. Several times a day, physicians are asked to come up with answers to various clinical problems in order to make

medical decisions. Questions that arise for most clinical situations are typically divided into two broad categories [36]:

- Quantitative questions, which aim to discover cause and effect relationships by comparing two or more individuals or groups based on differing outcomes associated with exposures or interventions.
- Qualitative questions, which aim to discover meaning or gain an understanding of a phenomena.

A more detailed categorization of clinical questions, based on their type and the respective study design that is most appropriate to provide answers, is presented in Table 1.1.

The questions that arise may be unstructured and complex at first, but it is important that they are translated in a clear form before proceeding to literature search. A good clinical question should be directly focused on the problem at hand and structured in a form that can be answered by searching the medical literature [37]. Without a well-formulated question, it can be impractical and very time consuming to search for and identify relevant evidence. Practitioners of EBM often use a specialized framework, called PICO, to form more focused and relevant questions [38]. PICO stands for Patient (or condition), Intervention (or diagnostic test or exposure), Comparison, and Outcome (or diagnosis/development/prevention of a condition). The PICO format can be expanded to PICOT, adding information about the Type of question being asked (for example therapy, diagnosis, prognosis) or the most appropriate study design for that particular question [39]. Notably, research has shown that the PICO format can help clinicians formulate more precise questions and develop more detailed search strategies [40, 41].

Identifying the Best Evidence

After having formulated an answerable and clinically relevant question, the next step is to track down the best available research evidence. In years past, searching for answers in the medical literature was a very daunting process, but nowadays the development of internet and large electronic databases has made searching and retrieval of information much easier. To further facilitate the identification of high quality evidence for a particular clinical problem, the EBM Working Group, in its guidance series, originally proposed a 4S model for ranking the quality and validity of various sources of evidence [24]. This 4S model has now been refined to a 6S pyramid that represents a hierarchy of six literature sources [42]. Similarly to the hierarchy based on study design, the quality of evidence increases as one goes up the pyramid. As illustrated in Fig. 1.3, the 6S pyramid begins with original primary studies and builds up to synopses of studies, syntheses (systematic reviews), synopses of syntheses, evidence summaries and systems [42].

When using the 6S model to retrieve research evidence, one should begin their search at the highest layer. Ideally this would be the "systems" layer, placed at the peak of the pyramid. "Systems" refer to computerized decision support systems, in which individual patient's characteristics are automatically linked (through

Table 1.1 Types of clinical questions and appropriate study designs

Type of question	Interpretation	Type of study
Treatment	How do we select among different treatments?	Randomized controlled trial
Diagnosis	How do we identify whether a person has a specific condition?	Randomized controlled trial or cross-sectional study
Prognosis	What is a patient's likely clinical course over time?	Cohort study
Etiology/prevention	How do we identify/prevent the causes of a specific condition?	Cohort study
Experiences	How does it feel to have a specific condition?	Qualitative study

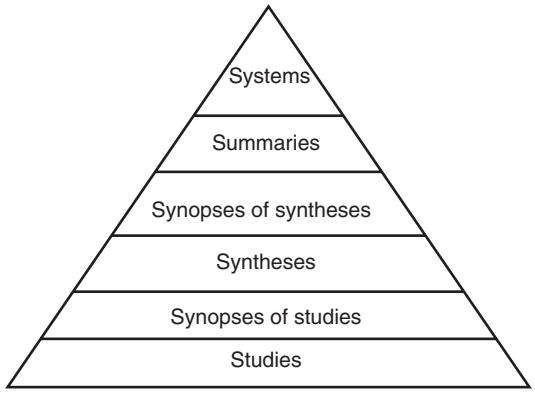

Fig. 1.3 The 6S pyramid of evidence sources

an electronic health record) to all important research evidence that are relevant to a specific clinical problem [43]. Subsequently, all key information is concisely summarized for clinicians in the form of patient-specific assessments or recommendations. However, to date few such systems are available, therefore one would need to look for "summaries" as the next best source. These "summaries" include pre-appraised resources of evidence that are regularly updated and integrate evidence-based information about specific clinical problems [42]. Such sources include DynaMed [44], UpToDate [45], BMJ Clinical Evidence [46] and BMJ Best Practice [47]. An additional type of pre-appraised summaries are clinical practice guidelines, provided they are based on comprehensive search and appraisal of the literature and report levels of evidence for each recommendation.

If a clinical question cannot be answered through a "summary", then a synopsis of a synthesis (systematic review) is the next stop. A good synopsis summarizes the main methods and findings of a high quality systematic review, providing sufficient information to support clinical action [42]. Such synopses are available in the Database of Abstracts of Reviews of Effects (DARE) [48] and in specific journals, including ACP Journal Club [49] and Evidence-Based Medicine [50]. Notably, other than systematic review summaries, these evidence-based abstraction journals also provide summaries of individual primary studies.

If more detail is needed or no synopsis is available, one should look for original systematic reviews or primary studies. These can be identified through search of electronic databases, such as PubMed, EMBASE and the Cochrane Library, by using relevant keywords (based on the PICO format of the clinical question) and specific study type search filters [51]. Finally, search engines like TRIP [52] or Epistemonikos [53] sort evidence across a broad range of various sources, including guidelines, structured summaries, systematic reviews and primary studies.

Critically Appraising the Evidence

Not all published research is good or even transferable to a particular patient. Therefore, the evidence retrieved from the literature search during step 2 must be critically appraised in terms of its quality (internal validity) and generalizability or applicability (external validity) [54]. Assessment of external validity of research findings is an issue regardless of the source of evidence, as it is related to whether the patient of interest differs significantly with the reference population, in terms of clinical or demographic characteristics, such as comorbidity, age, stage of disease, overall health status or concomitant medications. With regards to internal validity, it is reasonable to assume that evidence from most pre-appraised literature sources has been adequately peer-reviewed beforehand; however, this is not the case with primary research, such as individual studies, systematic reviews or even some guidelines. On this account, expert committees have issued formal guidance for optimal reporting for different types of studies. These are available at the EQUATOR website [55] and include CONSORT [56], STROBE [57], PRISMA [58] and RIGHT [59] statements for RCTs, observational studies, systematic reviews and clinical practice guidelines, respectively. In addition, useful tools for critical appraisal covering a wide range of research designs have been developed by the Critical Appraisal Skills Programme (CASP) and are freely available online [60].

Implementing the Results in Clinical Practice

The fourth step is perhaps the most complex, as it involves adjusting the evidence findings to the unique clinical circumstances, personal values and preferences of an individual patient. Under this premise, all relevant key evidence should be fully discussed during the clinical consultation, allowing for a therapeutic alliance to be formed between the patient and the clinician [37]. In particular, information should be tailored to patients' needs in order to permit meaningful deliberation and ideally facilitate shared decision making [31]. The shared decision making model has been seen as a mechanism of decreasing the informational and power asymmetry between patient and physician, by increasing patients' knowledge, enhancing their sense of autonomy and engaging them in making decisions, insofar as they wish to participate [61]. Shared decision making is increasingly advocated as an ideal model for most medical encounters and several countries have adopted policies that support its implementation within their healthcare systems [62]. It should be noted however, that shared decision making does not mean merely presenting the patient with a series of decision options alongside their respective advantages and drawbacks. Instead, real shared decision making involves introducing research evidence in a way that informs a dialogue about what matters to the patient, what is the best course of action and how this may affect the patient's well-being [63].

To facilitate this patient centered approach, a variety of tools for use during the clinical consultation have been developed for several medical conditions. According to a Cochrane systematic review, these decisions aids are "interventions that support patients by making their decisions explicit, providing information about options and associated benefits/harms, and helping clarify congruence between decisions and personal values" [64]. Two distinct types of decision aids have been described, patient decision aids (PtDAs) and conversation aids. Both types include a concise description of current research evidence about a medical condition and relevant treatment (or diagnostic) options, in a manner that can be easily understandable by patients [65]. However, while PtDAs aim is to improve patient knowledge and encourage patient involvement in decision making, conversation aids take this process one step further, by directly supporting and improving the quality of conversations that patients and clinicians have when making decisions together [66].

Evaluating the Overall Process

The fifth and final step involves evaluation our overall approach at frequent intervals in order to decide whether we need to improve any of the four steps. During this process, we need to ask whether we have formulated answerable questions, effectively identified and critically appraised the literature and integrated best available evidence with our clinical expertise and patient's values in the decision making [37]. In addition, it is also important to assess whether our overall approach has had a favorable effect on patient important outcomes. Interestingly, self-evaluation tools in practicing EBM are available online [67], while, according to a Cochrane systematic review, external audit and feedback on the practice of healthcare professionals can improve their performance [68].

The Importance of Evidence-Based Medicine

Despite its widespread recognition, EBM has also received criticism both by clinicians and researchers. However, as explained below, most of these criticisms are misperceptions, either of the definition of EBM or the way it should be practiced. Once cleared up, these misinterpretations highlight the benefits and importance of EBM.

Evidence-Based Medicine Is Superior to Experience-Based Medicine

Given that clinical practice has long been dominated by expert opinion and many guideline committees have used, and probably still use, expert consensus to make recommendations, one could argue that physiological reasoning and expert opinion should be the main drivers in clinical decision making. It has also been claimed that EBM does not represent a scientific approach to medicine and that reliance research evidence when making medical decisions, is problematic [69].

However, there are many examples where EBM, through the use of either RCTs or systematic reviews, has rightfully questioned unsubstantiated therapeutic claims of interventions that were later proven to be ineffective or even harmful [24]. It was only after the completion of RCTs, that administration of growth hormone in critically ill patients [70], ibopamine [71] and epoprostonol [72] in heart failure, and beta-carotene in patients with prior myocardial infarction [73] were associated with an increased mortality rate. Similarly, an RCT was necessary to establish the favorable effects of beta-blockers in reducing mortality in congestive heart failure, despite long-held beliefs that their negative inotropic action would be detrimental to these patients [74]. Well-conducted systematic reviews have equally contributed in improving the standards of healthcare [1]. Such examples include incorporating use of short course of oral steroids for community-acquired pneumonia [75] and establishing standards of care for early breast cancer [76]. Moreover, uptake of guidelines can have a major beneficial community effect, provided their development is supported by robust research evidence, as demonstrated by a decrease in asthma-related morbidity and mortality [77] and reductions in thromboembolic complications [78]. Of note, the Academy of Medical Royal Colleges in the United Kingdom has recently launched a booklet titled "Evidence based medicine matters", which contains 15 examples where EBM has benefited clinical practice in various medical specialties [79].

Evidence-Based Medicine Encourages the Development of Clinical Skills and Expertise

A common criticism of EBM is that it represents a "cookbook" in the sense that it regards clinical expertise mainly as a matter of collecting, analyzing and summarizing research done by others [80]. It has also been suggested that EBM, by encouraging blind adherence to guidelines, has shifted clinical decision making from the consultation room to the "professional association" [27].

Nevertheless, since the inception of EBM, its proponents have highlighted that external clinical evidence should not replace, but complement a physician's clinical intuition and judgement during the decision making process [13]. In fact, the original guidance series issued by the EBM Working Group underscore that a good understanding of the pathophysiological background of the disease in addition to clinical skills, such as careful history taking and physical examination, play a crucial part in the implementation of EBM [10]. Moreover, it is highlighted that teachers of EBM should be exceptional clinicians with a talent of precise observation, a gift for intuitive diagnosis and excellent judgment in making difficult management decisions [10]. Therefore, rather than diminishing the role of expertise and judicious clinical judgment, appropriate application of EBM values experiential thinking and encourages physicians to continuously improve or acquire new clinical skills. Even though some practitioners of EBM may also do research, it is important to remember that its practice is a method for providing care for patients and not a method for performing research [35].

Patients Are at the Core of Evidence-Based Medicine

Evidence-based medicine has also been accused that it disregards patients' unique knowledge and experience and ignores their needs and preferences [81]. Sweeney et al. suggest that EBM represents a doctor centered, rather than a

patient centered, approach, claiming that it focuses on the clinician's interpretation of the evidence and diminishes the importance of human relationships and the patient's role in decision making [82].

Again, these claims are inconsistent with the true definition of EBM. The practice of EBM strongly emphasizes the importance of adjusting the evidence to patients' preferences and incorporating their personal values and perspective into decision making. Moreover, shared decision making, albeit originally developed as a separate concept, is now being recognized as an integral component of the third principle of EBM [83]. Without shared decision making, authentic EBM cannot occur, since it is only through evidence-informed deliberations that patients can construct informed preferences and subsequently incorporate the evidence, along with their values and their clinician's expertise, into their decision making [83]. As a result, in recent years a lot of research has focused on how to effectively implement shared decision making using decision aid tools. Interestingly, a recent Cochrane systematic review has identified 105 RCTs of shared decision making tools, assessing 50 different decisions and involving approximately 31,000 patients [64].

Implementation of Evidence-Based Medicine Is Practical and Not Time-Consuming

It is true that certain skills, such as being able to identify and critically appraise research evidence, are prerequisites for effective application of EBM. On this account, one could claim that EBM is intended only for those few who have the time and resources to develop these skills and implement them in their daily clinical practice. This argument, often cited as the "ivory tower" concept, suggests that most busy clinicians are not able keep pace with the rapid advances in healthcare research and are unwilling to invest additional time in acquiring EBM skills [35].

To overcome these time-related barriers and facilitate faster retrieval of high quality evidence, EBM makes use of systematic reviews and more importantly of sources of pre-appraised evidence [42], which can be quickly assessed at the point of care [84]. Even when searching for primary studies is deemed necessary, use of certain search strategy guidance [51] or certain applications, such as PubMed Clinical Queries [85], can help save considerable time. Finally, according to survey studies, most physicians have shown interest in acquiring EBM skills [35], which can be done at any stage of the clinical training, even during medical school. In fact, a cross-sectional study has shown that early introduction of EBM in preclinical years was favorable for students and enabled them to critically apprehend and appraise new research findings and medical innovations [86].

Evidence-Based Medicine Makes Effective Use of Different Types of Research

EBM has been criticized for placing great focus on RCTs, resulting in lack of applicability in individual patients, as well as being largely industry driven [69]. However, these claims do not do justice to EBM. Although RCTs are usually considered the "gold standard" for establishing the effects of an intervention, EBM recognizes that other study designs are more suitable for providing answers about diagnosis, prognosis or harms [35]. Moreover, from its early days, EBM has acknowledged the necessity for individualization of care. In particular, EBM has provided guidance on the credibility of subgroup analyses and the effect of baseline characteristics on treatment outcomes [87]. Additionally, it has championed N of 1 trials, which are conducted in individual patients in whom the benefits and harms of treatments are uncertain [88]. Finally, EBM has given great consideration to issues related to researchers' conflicts of interest and industry's influence on the publication of research findings [89].

Uptake of Evidence-Based Medicine Can Improve Healthcare-Related Outcomes

It is reasonable for critics of EBM to ask for actual evidence that practicing EBM can actually improve patient outcomes [90]. However, assessing the effectiveness of EBM as a whole concept is most likely impractical, as it is not clear how to define "non evidence-based" medical practice, while it is also questionable whether withholding access to evidence from a control arm would be ethical [35]. However, research has been done on evaluating various individual steps of the EBM process, mainly related to identification or application of evidence retrieved from literature searches, and implementation of shared decision making.

In a cross-sectional study, rapid answering strategies based on searching PubMed and Epistemonikos proved feasible to implement by internal medicine clinicians and provided appropriate guidance for clinical questions [91]. In another study, 33 internal medicine physicians were presented with research information from standardized literature searches, after they had committed to a specific diagnosis and treatment plan for 146 inpatients [92]. Physicians changed treatment for 23 (18%) patients, while quality of patient care, as judged by an independent panel, improved in 18 (78%) of these patients [92].

Moreover, a study comparing hospitals with online access to UpToDate with other acute care hospitals, found that hospitals with UpToDate access were associated with significantly lower mortality and complications rates and a shorter length of stay [93]. In a similar retrospective study, in addition to reduced mortality and shorter length of stay, hospitals that had adopted UpToDate demonstrated higher quality performance across various inpatient quality measures for four common medical conditions [94].

Furthermore, a systematic review of studies that evaluated shared decision making, concluded that patients reporting that they had participated in shared decision making, are likely to enjoy better affective-cognitive outcomes, such as improved satisfaction and decisional comfort [95]. Finally, according to a Cochrane systematic review on decision aids, patients exposed to decision aids had better knowledge about treatment options and outcomes, felt clearer about their values, and were more likely to actively engage in decision making, in comparison to usual care [64].

Current Challenges and Future Implications

Despite its numerous achievements and benefits, EBM is not devoid of barriers or limitations. Leaders and proponents of EBM have highlighted that EBM is an evolving concept, and cautioned against its inappropriate use [29, 96]. Recently, a report summarizing the current challenges of EBM has been published in The BMJ [96], while a relevant website, named EBM manifesto [97], has been developed with the intention to encourage working groups to identify, suggest and implement solutions for better evidence and healthcare. Based on these data, the key challenges of EBM at its current state are mainly related to improving the quality and applicability of research and facilitating its efficient uptake in clinical practice.

A Call for Improving the Applicability of Primary Research

As mentioned earlier, an important disadvantage of RCTs is their limited generalizability in real-world patients, given that they recruit selected patients who fulfil specific eligibility criteria and are studied under a highly controlled environment. As a result, there is an increasing call from the medical and academic community for trials that produce more transferable findings to the daily clinical practice [98]. On this account, pragmatic trials have been proposed as a viable alternative to RCTs. Such trials are conducted under usual conditions, have broad inclusive criteria and offer practitioners considerable freedom in deciding how to apply the intervention or comparators of interest [99]. Pragmatic trials aim to answer the clinically relevant question of "which of two

(or more) treatments should we prefer" for our real-world patients, as opposed to traditional explanatory RCTs, which address "whether a difference exists between two treatments (one usually being a placebo) that are specified by strict definitions" [99]. Of note, specific tools related to both the design and critical appraisal of pragmatic trials have been developed [100, 101]. Notably, randomized registry trials are an innovative type of pragmatic trials that can further facilitate the incorporation or "real-world data" in primary research [102]. In a randomized registry trial, a clinical registry can be used to identify patients for enrolment, perform randomization, collect baseline variables, and detect end points. In comparison to traditional RCTs, they are inexpensive, less selective and enable fast enrolment and the possibility of very long-term follow-up [102].

A Need for More Patient-Oriented Research

Patient centered care may have acquired a prominent role in the healthcare agenda of various nations and medical associations, however considerable efforts are still required in order to determine what patients consider important and to ensure that their expectations are met by healthcare providers [31]. In addition to shifting the focus from clinically important outcomes to patient important outcomes [103], the field of patient-oriented care would be significantly enriched by qualitative research. Indeed, a lot of people in the EBM community acknowledge the utility of qualitative research in describing patients' experience and understanding their views [104]. Qualitative research can yield more valid information about subjective experiences, whereas a quantitative study might lose this depth and meaning [105]. In addition, information from qualitative studies may highlight important areas which require further quantitative assessment. Therefore, qualitative research should be viewed as complementary to quantitative research, and not as a type of study with lesser validity and robustness.

Moreover, despite the considerable progress that has occurred in the field of shared decision making during the last decade, current research has not yet established the link between shared decision making and patient behavioral or health outcomes [95]. Therefore, future studies should assess the impact of shared decision making across a continuum of outcomes and clinical settings and address the methodological challenges on how best to measure shared decision making [95]. Furthermore, it is unknown whether currently available decision aid tools can actually promote patient participation in making important healthcare decisions, other than merely presenting a summary of relevant research information [106]. On this account, future research should probably focus on designing more efficient and practical conversation aids that make intellectual and emotional sense to patients and encourage them to have meaningful conversations with their clinician [106].

Bridging the Gap Between Research and Clinical Practice

Engaging healthcare professionals in learning EBM and making it part of their clinical routine has always been one of the main challenges of EBM. To achieve a wider and more efficient uptake of EBM in daily clinical practice, physicians should be introduced to its principles at an early stage of their professional development, ideally during their medical training. Indeed, the need to develop a curriculum outlining the minimum standard requirements for training health professionals in EBM is now well recognized [107]. Other methods of teaching EBM to practice clinicians include morning reports, teaching conferences, and journal clubs [108]. However, EBM is best taught at the bedside, on the grounds that it is all about practicing medicine on actual patients at a real clinical setting and not about doing research. In addition, timely uptake and application of evidence-based knowledge requires, not only ready access to modern and high-quality information sources, but also efficient production and dissemination of both

systematic reviews and practice guidelines [109]. In turn, this can be accomplished by creating experienced research teams focused in producing rigorous evidence summaries and in developing electronic platforms that facilitate rapid updating of the medical literature [1].

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