Fundamental Concepts in Evidence-Based Medicine

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4.1 Introduction

Evidence-based medicine (EBM) practitioners consciously, deliberately, and consistently use the best current evidence to make patient care decisions. The evidence derives from clinical research, where randomized controlled trials (RCTs) are the best evidence. However, RCTs may not be appropriate in some situations, particularly in surgery, and important evidence may be obtained from other well-designed types of studies. Ideally, evidence synthesized in a methodologically correct way can help clinicians to make optimal treatment decisions in cross talk with the individual patient, taking into account the clinical situation and circumstances and patient values.

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4.2 Application of Research to Care Decisions

Evidence-based medicine (EBM) is "the explicit, judicious, and conscientious use of current best evidence from health care research in decisions about the care of individuals and populations" [1]. Both the term and the concept were developed by clinical epidemiologists at McMaster University [2], and the application of EBM has evolved over the last 20 years to become a central tenet and framework of good clinical practice. There are five steps to follow in practicing EBM: (1) Define the question or problem; (2) Search for the evidence; (3) Critically appraise the literature; (4) Apply the results; (5) Audit the outcome and give recommendations.

EBM advocates strongly believe that all stakeholders (patients, practitioners, health-care managers, and policy-makers) should consider the systematically collected and evaluated evidence from health-care research for application in decision-making. It is imperative that those findings meet multiple requirements, the most significant of which are to be empirically valid, reproducible, and ready for clinical implementation. This clinical decision-making process advocated by EBM practitioners appeared to oppose the traditional knowledge foundation of medicine, namely, the understanding of basic disease mechanisms coupled with clinical experience. This traditional method is illustrated by either the individual authority ("expert") or collective medical authority, such as a panel of experts, providing practice guidelines based on expert opinion. EBM claims that experts are more fallible in their recommendations regarding the optimal treatment of a condition than evidence derived from sound systematic observation (i.e., health-care research). This may be especially true for recent decades, as new applied research methods have been developed for observation and experimentation in increasingly complex clinical settings. Applied research methods are based on probabilities for relationships and the effects of interventions, rather than underlying mechanistic explanations. As such, practitioners must be ready to accept uncertainty and acknowledge that appropriate management decisions can be, and often are, made in the face of relative ignorance of their underlying nature.

While advocates currently urge widespread use of the concept and techniques in clinical settings, the initial intention of EBM was educational, to train residents to become better physicians. This was consistent with the philosophy underlying the unique approach to medical education at McMaster's nascent M.D. program and the university's focus on innovation in education. It also recognized that physicians in a busy practice have limited time to peruse the literature and the training was focused on efficient methods for extracting information from literature in a timely fashion. Today, physicians are able to locate information to an incredible extent through the Internet and associated electronic searching capabilities of databases, which allows the regular application of EBM in daily practice to an extent not envisioned by its pioneers.

A fundamental assumption of EBM is that practitioners whose practice is based on an understanding of evidence that has been validated experimentally and statistically will provide superior patient care compared with practitioners who rely solely on knowledge of pathophysiology and their own clinical experience. There is no current evidence to this effect, only multiple published trials whose conclusions contradict conventional wisdom. Nevertheless, the New York Times Magazine "Year in Review" included EBM as one of the most influential ideas of 2001 [15]. It has been extensively written about, and multiple user guides to critical appraisal have been published (JAMA's Oxman et al. [3] and Bhandari's series [4–7] among others), illustrating the interest of the medical community as a whole.

Surgical practices have evolved over the years mostly based on single center and even single eminent surgeon innovations. The same disease is managed, and operated on, differently between centers or even between individuals, depending on convictions derived from hierarchical surgical training. Surgical procedures are constantly undergoing minor changes and being refined, each surgeon making small adjustments or innovations that suit their approach to the problem at hand. Major technical innovations

still tend to be reported as case series, which still, unfortunately, form the core of the clinical surgical literature. New operation techniques have appeared without rigorous scrutiny or methodologically sound comparison with the previous preferred clinical management approaches. Indeed, surgeons have been accused of being early adopters and enthusiasts and criticized for not evaluating new procedures, techniques, and technologies, as one would in a new drug. Spodick argued for an "FDA for the surgeon" [8, 9] in relation to these concerns.

4.3 Patient Values and Preferences in EBM

Despite increasing acknowledgment of its importance, some opponents continue to criticize EBM as focusing on populations while neglecting the individual [10, 11]; however, the most updated definition of EBM states that it is the integration of the best available research evidence, our clinical circumstances, and patients' values and preferences. Bassler et al. [12, 13], in their two-part commentary, describe EBM tools that address individual patient decision-making (Tables 4.1 and 4.2). The EBM still relies on aspects of the traditional approach to decision-making – that is, the clinician's expert thinking and expert ability to assess the clinical situation and patient values – while complementing it with a set of rigorous tools. These expert skills allow the physician to tailor the application of study findings, often derived from randomized controlled trials (RCT), to the individual, and to quantify the benefits and risks of a particular treatment decision for a particular patient [12]. The extent to which individual patients want to be involved in decision-making varies, and a primary responsibility is to establish the patient's wishes in this regard [13]. It is clear that evidence alone is inadequate for making medical decisions for individual patients and that each patient's (and perhaps society's) values need to be taken into consideration and that the choice of treatment must involve both patient and physician.

Several evidence-based approaches are available for providing shared decision-making support, including formal clinical decision analysis and patient decision aids [14]. Formal clinical decision analysis, which incorporates the patient's likelihood of the outcome events with his or her own value for each health state, is complex and time-consuming, though it may become feasible in clinical practice [15]. The initial response from groups of expert physicians was to work toward the establishment of management recommendations, or clinical guidelines. Despite their growing importance, their adoption has encountered significant resistance among clinicians. A group from Boston Children's Hospital developed Standardized Clinical Assessment and Management Plans (SCAMPs) as an innovative, clinician-led approach to building, implementing, and constantly improving flexible guidelines. Their implementation is underway in multiple medical and pediatric subspecialties, and further research on their acceptability by physicians is underway. For now, patient decision aids are more realistic in current practice. They present management options and associated outcomes in ways that are understandable to patients. They also succeed in integrating the associated complexity associated with those choices. There is a wide range of decision aids available that address a variety of health-care problems; for example,

Table 4.1 Criteria to consider when applying the results of research studies to individual patients [12]

Patient characteristics	Health-care characteristics	Outcome characteristics
Biological factors (sex, comorbidities, race, age, severity of pathology) Patient compliance with treatment requirements	Compliance of health-care providers with treatment requirements Resources available for implementation (e.g., availability of monitoring) Expertise of clinicians	Did the study measure an outcome of importance to the individual patient?

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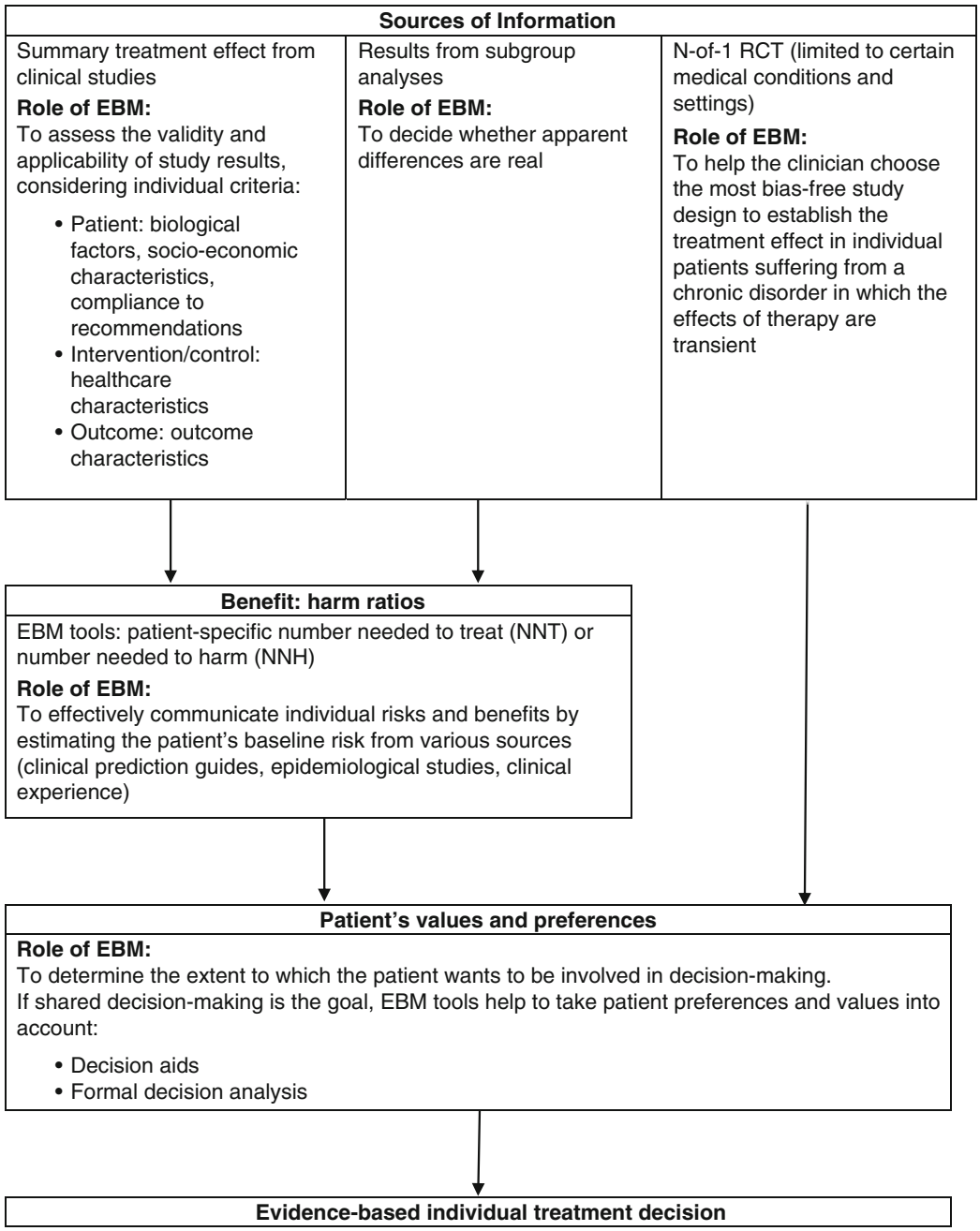
Table 4.2 The process of individualized evidence-based medical (EBM) decision-making [13]



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see the Internet-based collection at Ottawa Patient Decision Aids (http://decisionaid.ohri.ca/). Trials indicate that those decision aids enhance active patient participation in decision-making and improve agreement between values and choice [16], in the spirit of EBM.

Clinical decisions must, firstly, include evaluation of the patient's clinical and physical circumstances, to establish a diagnosis and obtain a range of available treatment options. Secondly, a more complete analysis is conducted, which identifies evidence concerning the efficacy, effectiveness, and efficiency of the available options. Thirdly, given the likely consequences associated with each option, the clinician must consider the patient's preferences (in terms of what risk-to-benefit ratio she or he would tolerate). Finally, clinical expertise is needed to bring these considerations together and make a treatment recommendation that is acceptable to the patient.

The term evidence-based medicine was developed to encourage practitioners and patients to consider – no more, no less – current best evidence in making decisions. An alternative term that some may find more appealing is research-enhanced health care. Whichever term is applied, one can be confident in making better use of research evidence in clinical practice [17].

4.4 Levels of Evidence and Their Importance

Systematic reviews of randomized trials represent the highest quality evidence, whereas observational studies are mostly considered to generate lower-quality evidence (Fig. 4.1) [18]. Quality may be downgraded as a result of methodological limitations (study design or implementation), imprecision of estimates (wide confidence intervals), variability in results, or publication bias. Quality may be upgraded because of a very large magnitude of effect, a dose-response gradient, or if all plausible biases would serve to reduce an apparent treatment effect. Presence of critical outcomes determines the overall quality of evidence. Evidence profiles provide simple, transparent summaries [19]. The proper use of evidence-based

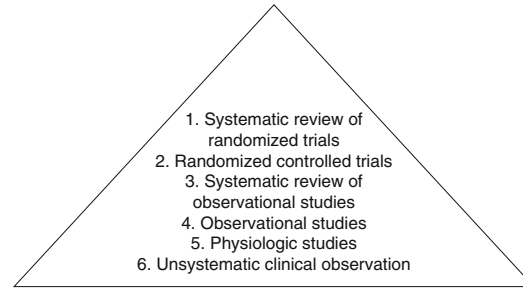

Fig. 4.1 Hierarchy of evidence (Montori [18] Reproduced from Copyright 2002 with permission from Elsevier)

information is not the sole strict adherence to RCTs, but more accurately, the informed and effective use of all types of evidence.

In January 2003, the editorial board of the American edition of the *Journal of Bone and Joint Surgery* adopted a level of evidence rating system [20] developed at the Centre for Evidence-Based Medicine at Oxford University (Table 4.3) [21]. It must be remembered that current concepts around levels of evidence and critical appraisal are based on a medical model, and surgical studies have unique issues that may be better dealt with in an evidence-based surgical model [22]. The nature of a surgical intervention introduces challenges around selection and observer bias, blinding, standardization of technique, learning curve, generalizability, prevalence of the problem, and patient and surgeon equipoise [22]. The numbers of patients with a particular surgical pathology are low, so the evolution of surgical research methodology will necessitate collaboration between different sites and surgeons in order to increase the level of evidence of the selected designs. Surgical research is complex and, as a result, the research question framed by the above surgical considerations determines the best study design. In other words, strong recommendations can be based on lower levels of evidence if the question and circumstances dictate it [23]. The suggestion that RCTs are the only acceptable design is an overly narrow view and lacks insight as to the relative strengths of the different methods [24]. One recognizes that a well-done observational study, with minimal biases and a significant effect, may be of more sound quality and its conclusions

Table 4.3 Levels of evidence (OCEBM levels of evidence working group 2011)

Question	Step 1 (Level 1[a])	Step 2 (Level 2[a])	Step 3 (Level 3[a])	Step 4 (Level 4[a])	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances[b]	Local nonrandom sample[b]	Case series[b]	n/a
Is this diagnostic or monitoring test accurate? (diagnosis)	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Individual cross-sectional studies with consistently applied reference standard and blinding	Nonconsecutive studies, or studies without consistently applied reference standards[b]	Case-control studies, or poor or non-independent reference standard[b]	Mechanism-based reasoning
What will happen if we do not add a therapy? (prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial[c]	Case-series or case-control studies, or poor quality prognostic cohort study[b]	
Does this intervention help? (treatment benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Nonrandomized controlled cohort/follow-up study[b]	Case-series, case-control studies, or historically controlled studies[b]	Mechanism-based reasoning
What are the *common* harms? (treatment harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Nonrandomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms, the duration of follow-up must be sufficient)[b]	Case-series, case-control, or historically controlled studies[b]	Mechanism-based reasoning
What are the *rare* harms? (treatment harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (screening)	Systematic review of randomized trials	Randomized trial	Nonrandomized controlled cohort/follow-up study[b]	Case-series, case-control, or historically controlled studies[b]	Mechanism-based reasoning

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[a]Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size

[b]As always, a systematic review is generally better than an individual study

[c]OCEBM Levels of Evidence Working Group – Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard, and Mary Hodgkinson

Table 4.4 Types of study design and their advantages and disadvantages [25]

Type of study	Type of design	Advantages	Disadvantages
Observational studies	Case report	Used for rare clinical events	No comparison group
	Case series	Experiences with new or complex treatments	No comparison group
	Cohort studies	Resemble "real-life" clinical situations	Prone to confounding
	Case-control studies	Small sample size and short duration	Prone to confounding and bias
Experimental studies	Randomized controlled trials	Avoidance of confounding	Expensive
			Limited generalization
			Difficulties in study recruitment and conduct

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more reliable and generalizable than the conclusions drawn from a poorly conducted RCT.

Capable clinicians need to understand the importance of developing an appropriate research question. Study design and appropriately selected outcomes are also key to selecting and applying the best available evidence to patient care (Table 4.4) [25]. Furthermore, they should recognize that treatment recommendations are not only based on critical appraisal and levels of evidence but also reflect the risk-and-benefit ratio and cost. Health policy-makers, editorial boards, granting agencies, and payers should understand that EBM, especially as it pertains to surgical specialties, is not always best represented by a RCT. They must realize that the question being asked and the research circumstances dictate the study design. Finally, the role of clinical expertise and informed patient preference in EBM needs to be acknowledged, as it provides the generalizability so often lacking in controlled experimental research [25].

4.5 Management Recommendations: EBM

As per McMaster grading system, the strength of any recommendation depends on two factors: the trade-off between benefits and risks and the quality of the methodology that leads to estimates of the treatment effect. This approach to grading recommendations captures the magnitude of random error in the decision about the confidence in the trade-off between benefits, harms, and cost (Table 4.5) [26]. The uncertainty associated with this trade-off will determine the strength of recommendations. The grades that experts will generate using the McMaster approach are 1A, 1B, $1C^+$, 1C, 2A, 2B, and 2C (Table 4.5) [26]. If, based on the available evidence, experts are very certain that benefits do, or do not, outweigh harms and cost, they will make a strong recommendation – in the McMaster formulation, Grade 1. If they are less certain of the magnitude of the benefits and harms, and their relative impact, they must make a weaker Grade 2 recommendation. Grade 2 recommendations are those in which variation in patient values or individual physician values will often mandate different treatment choices, even among average or typical patients. The McMaster approach expresses the primacy of the benefit versus harm judgment by placing it first in the grade of recommendation.

The assignment of Grades A to C, the second part of the grade, depends on the possibility of bias based on the methodological quality of the underlying evidence. The approach classifies randomized controlled trials with consistent results as Grade A. If results across randomized trials are inconsistent, or if trials have major methodological weaknesses, one assigns a Grade B rating. Evidence leading to Grade C recommendations comes from observational studies and from the generalization of results from randomized trials in one group of patients to a

Table 4.5 Current approach to grades of recommendations [26]

Grade of recommendation	Clarity of risk/benefit	Methodologic strength of supporting evidence	Implications
1A	Clear	Randomized trials without important limitations	Strong recommendations; can apply to most patients in most circumstances without reservation
1B	Clear	Randomized trials with important limitations (inconsistent results, methodologic flaws[a])	Strong recommendation; likely to apply to most patients
1C+	Clear	No RCTs, but RCT results can be unequivocally extrapolated from observation studies	Strong recommendation; can apply to most patients in most circumstances
1C	Clear	Observation studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	Randomized trials without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	Randomized trials with important limitations (inconsistent results, methodologic flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observation studies	Very weak recommendation; other alternatives may be equally reasonable

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Since studies in categories B and C are flawed, it is likely that most recommendations in these three classes will be Level 2. The following considerations will bear on whether the recommendation is Grade 1 or Grade 2: the magnitude and precision of the treatment effect, the patients' risk of the target even being prevented, the nature of the benefit, the magnitude of the risk associated with treatment, variability in patient preferences, variability in regional resource availability and health-care delivery practices, and cost considerations. Inevitably, weighing these considerations involves subjective judgment
[a]These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, and with large loss to follow-up

different group, as illustrated by Table 4.5. When experts feel confident about the generalization of the conclusions from randomized trials to another population or find the data from observational studies is overwhelmingly compelling, they choose Grade C+.

We believe that most criticism of evidence-based medicine results from a misunderstanding of its purpose and process. As previously stated, only through a thorough, exhaustive, and critical appraisal of the evidence the practitioner can make valid and informed judgments about interventions. This evidence base, together with clinical expertise, allows to incorporate patient's values and preferences in the decision-making process.

Another frequently encountered misconception is that only randomized controlled trials or systematic reviews constitute the evidence in evidence-based medicine. One must remember that EBM emphasizes the consideration of evidence from various types of studies, appropriate for different clinical questions, including everything from observational studies to meta-analyses.

4.5.1 Limitations of Evidence-Based Medicine

There are limits to what evidence-based medicine can address. Literature cannot be interpreted in the absence of common sense and clinical experience. A frequently cited example of the inappropriate application of evidence-based medicine techniques is the assertion that there is

no scientific evidence on the effectiveness of parachute use for life preservation following falls from aircraft [27]. Indeed, no randomized controlled trial (RCT), or even a well-designed cohort comparison, has ever been performed to provide such evidence. But who would conclude that, in absence of evidence to this effect, they would rather not wear a parachute? For the sake of completeness, let us mention that there are case reports of survival following falls without parachutes and reports of deaths in skydivers using parachutes. One must remember that a treatment, which is not supported by high-quality medical evidence, does not mean that the treatment has no value. The Cochrane group considers only randomized controlled studies as valid sources of medical evidence. The absence of such studies, in their opinion, equates with an absence of evidence. However, as Doug Altman declared, "absence of evidence is not evidence of absence" [28]. There may be multiple reasons for the absence of evidence, from the complexity to the prohibitive costs of performing a methodologically sound RCT, or to the biases inherent to the intervention under scrutiny. In these cases, other types of quality clinical research (such as observational studies) may provide useful information.

4.6 Why Is Evidence-Based Medicine Important to Spine Surgeons?

Bridwell et al. performed an analysis of the current status of evidence for primary adult spinal deformity correction to answer the question of whether surgical treatment benefits patients [29]. They concluded that the majority of smaller studies suggest that surgical treatment benefits the patient. However, there is no multicenter prospective randomized study to answer this question.

There are many areas of spine surgery practice where the redefinition of the state of current evidence would be useful. The first, and probably the most difficult, would be an evaluation by systematic review of the different operative approaches already in clinical practice. For example, does the wide variation in surgical approaches for correction of primary adult spinal deformity make a difference? The large number of different surgical techniques testifies to the reality that in many situations, the technique probably does not matter as much as one would think. Such questions often raise strenuous, and occasionally acrimonious discussions in support of one operation over another. There may be a "best solution" in the hands of the "best surgeon," but it is not clear if such a hypothetical "best" surgical technique can be done successfully by every surgeon. A less complicated operation may serve patients better when done successfully by most surgeons [22]. It is important for surgeons to not only adhere to the best evidence in managing their patients but, more importantly, to know their limitations and comfort zone for using a new technology.

4.6.1 Where to Start with Evidence-Based Spine Surgery?

If one wants to dive in EBM in a field relatively new to this discipline, it can be difficult to know where to begin. One has to elaborate a clear research question, and go on from there, starting with already available knowledge on the topic. In addition to expert opinion, a physician searching for understanding would be influenced by his knowledge of experimental physiology. Understanding about how the body functions and reacts is derived from laboratory experiments designed to validate or invalidate hypotheses. This scientific method is the basis for research in the biological, physical, and chemical sciences. The manner in which medical knowledge accrues has changed over time. As Geoff Watts has written: "Knowledge doesn't suddenly appear in neat and tidy quanta. Like patches of lichen spreading over a rock face, it accretes over decades" [30]. Each key development is built upon earlier ideas.

Clinical trials are not a recent research tool. There is actually evidence of what may be the

first clinical trial in the biblical book of Daniel. Neuhauser and Diaz [31] provide a refreshing look at the original clinical trial in their 2004 article on the topic. Example of other famous trials that were conducted in the eighteenth century focused on scurvy and smallpox. These types of trials slowly made their way into the medical literature. Initially, most trials included only a few patients and sometimes produced conflicting or inconclusive results. The same is true today in the surgical literature. Critical appraisal was born initially from the necessity to assess and improve the methodological quality of research, in order to draw appropriate conclusions from the literature.

Meta-analyses were developed in social sciences around the same time, as a quantitative tool to combine and synthesize findings from a large number of smaller studies, hoping that the data, when considered as a whole, would either support or dispel a hypothesis. The importance of meta-analyses in medicine was identified by Chalmers et al. [32], where the pooling of individual studies together increases the power and builds a meaningful body of evidence on a topic. They are now increasingly carried out in medicine and provide one of the highest levels in the hierarchy of evidence. Of importance is the establishment of the first Cochrane Centre, in response to Archie Cochrane's comment about the medical profession not having created a database of published clinical trials according to specialty, to be constantly updated. The Cochrane Collaboration publishes systematic reviews that are considered of high methodological quality, and their handbook is a key tool for whoever is interested in conducting systematic reviews.

All of the abovementioned tools – experimental physiology, clinical trials, and meta-analyses – can contribute to clinical decision-making in spine surgery; however, the quality of the evidence from each of these sources differs. An EBM practitioner would rely more on meta-analyses than physiological studies in regard to patient care decisions and would additionally consider the clinical situation and patient values along with clinical evidence in making patient recommendations for treatment.

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