CHAPTER 1

EVIDENCE BASED MEDICINE IN ORTHOPEDICS

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In 2007, the British Medical Journal (BMJ) reported the fifteen most important medical milestones since its beginning in 1840. Included were the discovery of DNA, the development of vaccinations and of antibiotics, the use of anaesthetics for surgery, and Evidence-Based Medicine (1).

Although definitions vary, as suggested by Sackett et al., Evidence Based Medicine is the *"conscientious, explicit, and 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, patient's values and preference with the best available external clinical evidence from medical literature (2).

Evidence based medicine is not "cookbook" medicine. Any external guideline must be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament, and preferences, and thus whether it should be applied (2).

The trend that includes these principles was first started by Gordon Guyatt and the group that he founded at McMaster University in 1992. In fact, that is the year of the appearance of a series of articles in the Journal of the American Medical Association (JAMA), from which originated a long series of articles later collected in books becoming bestsellers (3).

Different factors have contributed to the increasing importance of Evidence Based Medicine:

- The need for constant daily reading to acquire relevant information about diagnosis, treatment and prognosis of the disease by physicians;
- Lack of update of the traditional sources of medical information, which are often outdated, of poor quality and above all in an overwhelming volume;
- Discrepancy between increasing clinical experience, and decreased awareness of the scientific studies;
- Little time for clinicians (minutes per week) to read and review work.

EBM requires that choices and decisions are made by critically reading and reviewing the literature, by assigning value and weight to the specific research methodologies reported in the studies, by the scientific validity of the work and the techniques used by the researcher. A more critical approach concerning the changes that must be made in medical practice is also necessary. This discipline involves the use of the best evidence by assigning a higher value to the well-conducted and well-executed clinical studies, and a lower value to the expert opinions and uncontrolled observational studies, such as "case reports" and "cases series". It is important to remember that the EBM approach has five basic steps which, as they are completed,

Key words: Evidence Based Medicine, Evidence Synthesis, EBM approach

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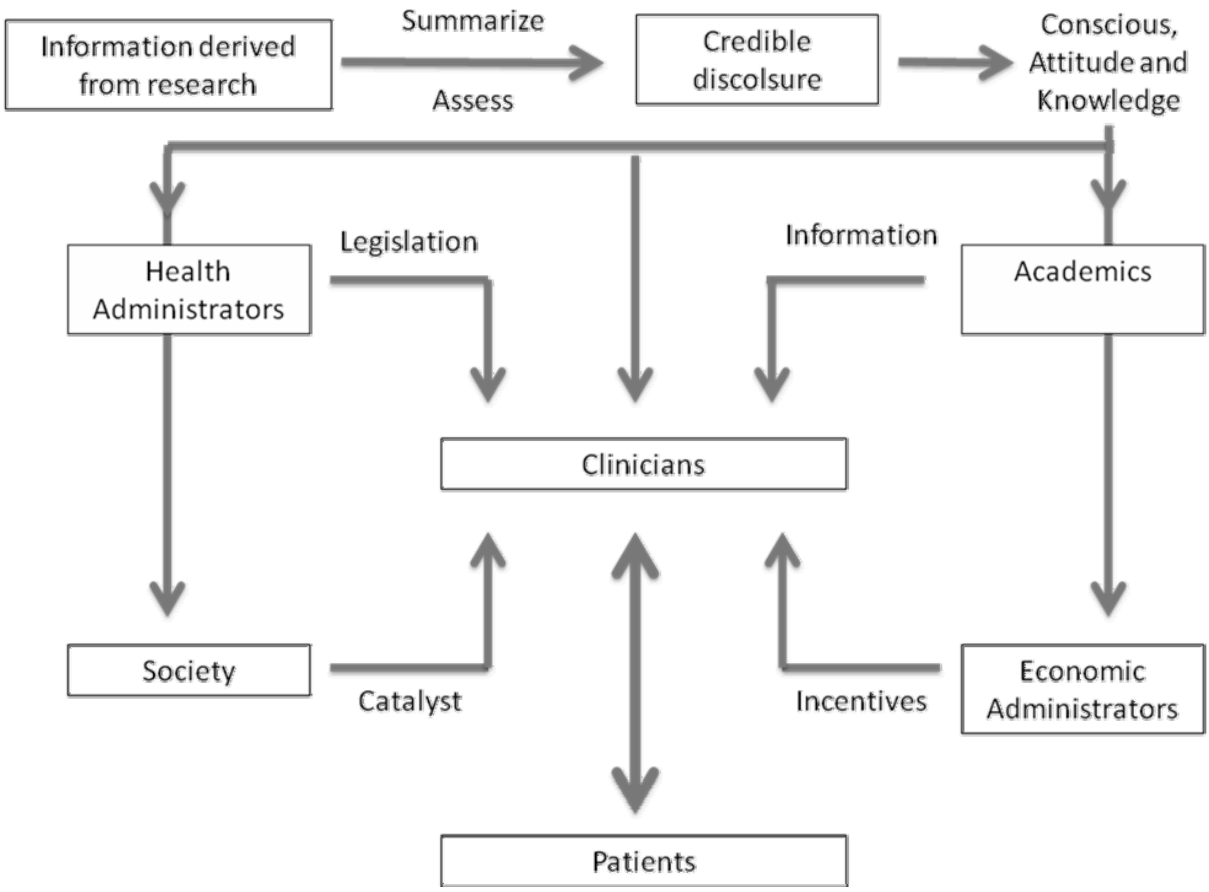

Fig. 1. *Disclosure model. Translated from Liberati A. Etica, Conoscenza e Sanità. Il Pensiero Scientifico Editore. 2005.*

have the ultimate goal of extracting evidence (4):

1. Formulation of unanswered questions;
2. Collecting evidence;
3. Evaluation of evidence;
4. Implementation of evidence;
5. Analysis of the process.

The benefits of EBM are designed to help doctors faced with an excessive amount of information, reduce inequality in care, reduce healthcare costs and justify the choices of treatment for an audience (5-6).

However, the definition of what we accept as "evidence" is complex for a number of reasons, both in clinical research and orthopedic practice.

These include a general lack of knowledge, a tendency to vigorously defend long-established procedures, the learning curve issue, the difficulty in blinding and the ethical considerations (7). How many surgeons are there who are willing to abandon a technique they know well and with which they have obtained good results for another they do not know, even if it has been demonstrated that it offers excellent results? We may be among those!

Unluckily, the presence or absence of evidence is never clearly defined because for many clinical practices only filtered information is available as the results from different studies do not always agree; in other cases the information that we need is not available because the necessary studies have not been performed or the quality of the trials carried out makes them not easily interpretable (8).

Many factors, not always positive, have contributed in recent years to the growing interest, not always impartial, in EBM: there were those who saw it as a

useful means for cutting health care costs (9), those who saw it as a tool to oppose the too dogmatic and authoritarian medicine, and finally those who wanted to turn the trend in an oversimplified epistemological scenario without any complex analysis.

The principles of Evidence-Based Medicine should be used in a systematic way to review medical information, the production of specific articles and presentations at meetings. Orthopedic surgeons must first identify clearly and unambiguously the validity of the information and only then decide whether they change their surgical practice (Fig.1).

The recognition of the value of EBM represents an important step in developing a complete and coherent method for to practice that is clinical medicine. (10)

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CHAPTER 2

STUDY DESIGN IN CLINICAL RESEARCH

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"The Design of Experiments" (1935) by Ronald A. Fisher is the first book written about the systematic design of experiments. Since 1935 epidemiology has strided ahead. In the past few years, especially from the 1990's onwards, the application of epidemiological principles has lead to the characterization of evidence methodology. The different clinical studies can be classified on the basis of the purpose and the methodology of research. The quality of the studies must always be evaluated on the basis of the reproducibility of the results and of the conclusions that can be drawn.

Division into large research study groups according to type:

1. Traditional Sources;
2. Primary Research;
3. Secondary Research (Fig. 1).

Traditional Sources

Traditional sources are books, narrative reviews, editorials, i.e. a quantity of information containing a mixture of evidence and opinions and no critical or systematic methodology. When we do seek knowledge from traditional sources of information such as journals and text-books, they are often either too disorganized or out of date (1). Without a doubt, however, they can be quite pleasant to read, and may often give us a general idea of topics that we do not know. They are not considered models of evidence-based medicine.

Primary Research

This group is divided into two categories according to the methodology used:

1. Observational Studies;
2. Experimental Studies.

1. Observational Studies

Studies in which different actions or natural exposure are analyzed to gain an understanding of the effects on health outcomes. These in turn are split in to:

a. Descriptive Studies. These studies have an "Anecdotal Evidence" because they do not have a control group. Such evidence is not seen as conclusive, it is as an invitation to a more rigorous scientific study of the phenomenon in question (2). They are divided in to:

- Case Reports: a detailed description of the symptoms, signs, diagnosis, treatment and follow-up of an individual patient. They usually cover one of the following: an unexpected event following a specific treatment, a rare or unique disease, new therapeutic approaches, anatomical variations, unusual symptoms of a given disease etc. Case reports should be short and focused, with a limited number of figures and references (3).
- Case Series: these regard patients with

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a known exposure, given similar treatment, or examines them for exposure and outcome. It can be retrospective or prospective and involves a smaller number of patients. Case series may be consecutive or non-consecutive, depending on whether all cases presented over a period were included, or only a selection of these.

b. Analytical Studies or Comparative Studies are studies that draw inferences about the possible effect of a treatment on subjects, where the assignment of subjects into a treated group versus a control group is beyond the control of the investigator, i.e. there is no intervention by the investigator (4). These are divided in to:

- Case-Control Study: a study of patients with an outcome variable of interest and a suitable control group of persons without it. The potential relationship of a suspected risk factor is studied by comparing the control group and the case group with regard to how frequently the factor is present. The case-control study used to be called "retrospective" because, conceptually, it goes from disease onset back to the postulated causal factors. The association between the risk factor and the disease is expressed by measuring the Odds Ratio, i.e. the ratio between the number of times in which the event occurs and the number of times in which the event does not occur.
- Cohort Study: a study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed in different degrees to factors believed to influence the occurrence of an outcome. The main feature of the cohort study is the observation of large numbers of subjects over a long period, comparing the incidence rates in groups that differ in exposure levels, for this reason they used be called "prospective" studies. (5) The association between the disease and the risk factor is expressed, in this case, by the risk ratio, i.e. the ratio between the risk in the exposed group and the risk in the unexposed group .
- Cross-Sectional Study: a study that investigates the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at a given time, like a snapshot. So the temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study. Usually the value of prevalence is estimated.
- Ecological Studies: studies in which the units of analysis are a populations or group of people rather than individuals. Conclusions of ecological studies may not necessarily apply to the individual hence they are unpopular in clinical practice (6).

Whether conducting a cross-sectional, cohort, retrospective or case control study, the difference between the prevalence and incidence of cases can be sought.

The *prevalence* of cases reflects the population that is diseased at a specific time and includes all those cases that exist in the population as well as all those new cases that arise during the time interval measured. Since the prevalence of cases includes people who have had the disease for some time and those who have contracted it recently, the factors associated with exposure include both risk factors associated with the actual development of the disease as well as protective factors.

Instead, the *incidence* reflects the new cases that develop in a population during a specific period of time. Factors associated with the incidence reflect only the risk of developing of the disease or the outcome of interest.

Prospective cohort studies generally provide strong evidence but they are often not feasible because of their cost, the difficulty in finding the same study sample and the need to have a long follow-up. They also often involve considerable ethical implications, such as monitoring or following people who are suffering from an unknown disease. Therefore, historical or retrospective cohort studies and case-control studies are the most commonly used in the research of risk factors, especially in orthopedics.

Experimental Studies

This is a study in which the investigator intentionally alters one or more factors while keeping constant other study conditions in order to analyze the effects.

These can be split in to uncontrolled trials or controlled trials depending on whether or not there is a control group.

a. Uncontrolled Trials are also called pilot studies, and are usually conducted when a controlled study is not feasible, both for economic and/or ethical

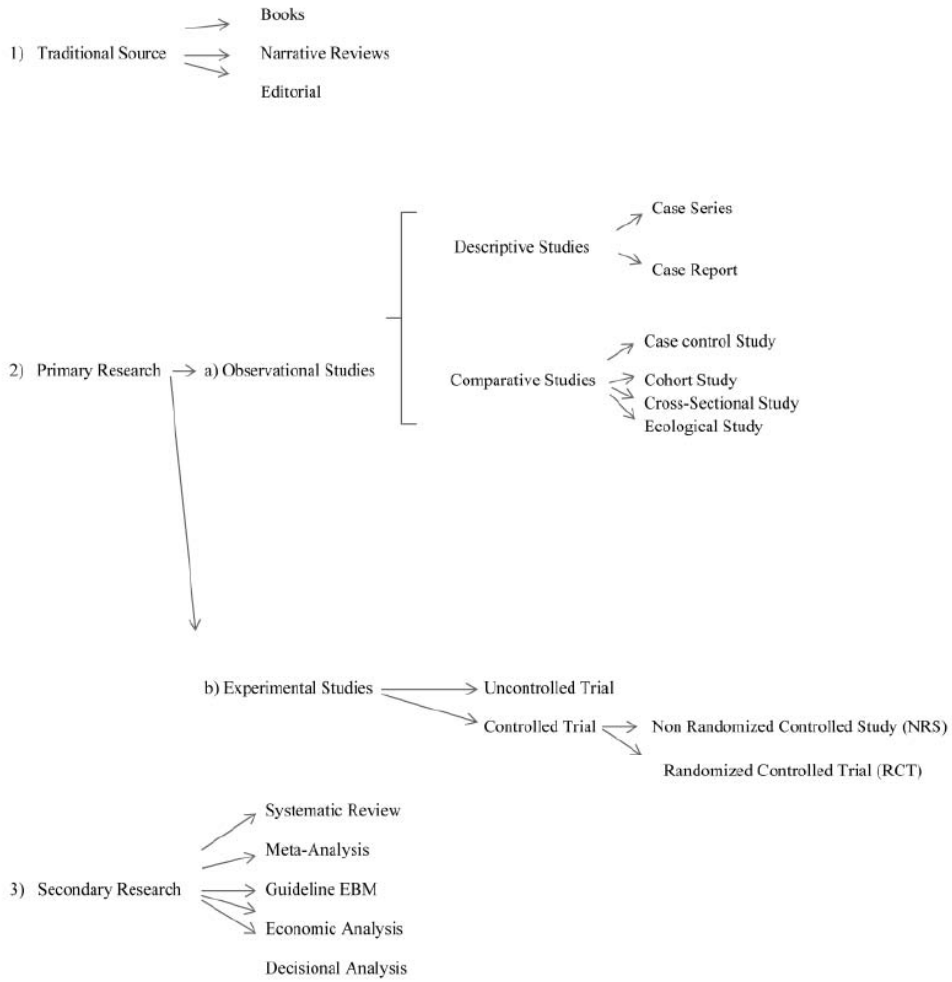

Fig. 1. *Classification of studies in clinical research.*

reasons.

b. Controlled trials instead can be either randomized or non-randomized.

- Non-Randomized Controlled Study (NRS): is an experimental study in which people are allocated to different interventions using methods that are not random. The importance of randomization was emphasized by Charles Peirce in "Illustrations of the Logic of Science" (1877–1878). Randomization-based inference is important in experimental design and in survey sampling. Since the days of Austin Bradford Hill and his famous book, Principles of Medical Statistics (1961), non-randomized clinical trials express poor evidence so these studies are usually used as pilot studies. This group includes also ***"****Controlled before-and-after study"* in which observations are made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not; the ***"****Interrupted time series study"* is a study that uses observations at multiple time points before and after an intervention (the so-called 'interruption'). The design attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time; and the ***"****Historically controlled study"* i.e. a study that compares a group of participants receiving an intervention with a similar group from the past who did not.

- Randomized Controlled Trial (RCT): is a trial in which subjects in a population are randomly allocated into groups, usually called study and

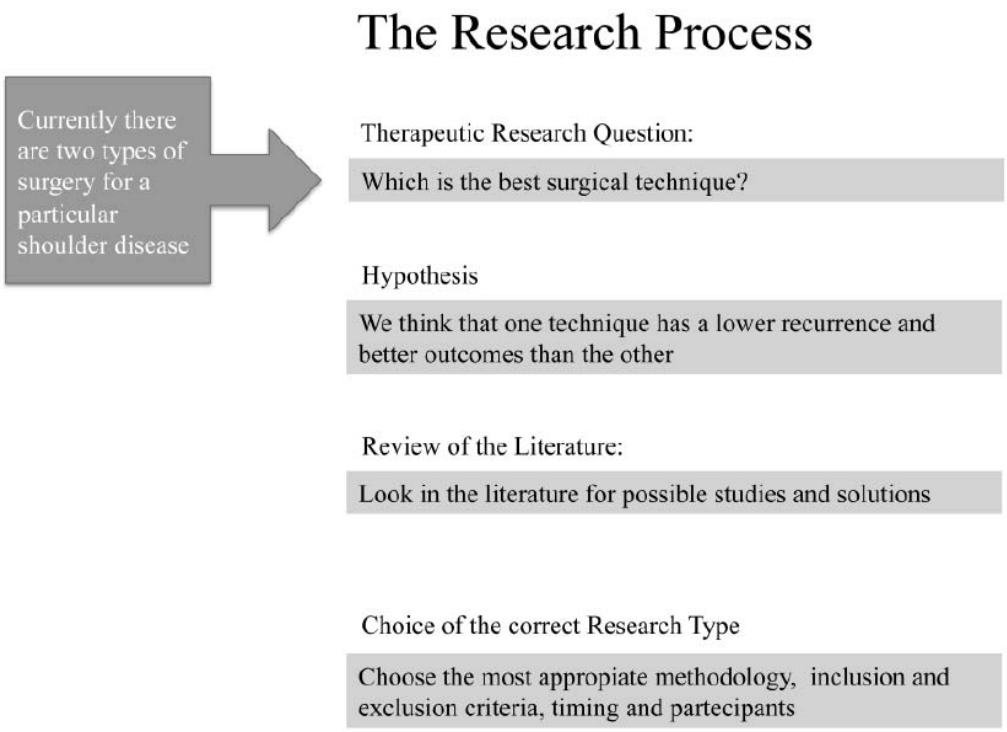

Fig. 2. *The Research Process.*

control groups, to receive or not an intervention. The results are assessed by rigorous comparison of rates of outcome in the study and control groups. RCT are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology and medicine.

Secondary Research

This involves the summary, collation and synthesis of existing researches, where data is collected and critically appraised based on a systematic approach of assessment.

1. Systematic reviews and Meta-Analysis;
2. EB Guidelines;
3. Economic analysis;
4. Decisional analysis.

1. Systematic Reviews (S.R.): is the application of strategies to gather, critically appraise and synthesize all relevant studies on a specific topic, focus on peer-reviewed publications about a specific problem using a rigorous standardized method for selecting and assessing articles. Systematic reviews are not all equal, and quality issues are important, methodology of research and analysis must be rigid and clear. The S.R. may be a Meta-Analysis if it includes a quantitative summary of the results (7-8).

2. Evidence Based Guidelines: is a statement about a defined task or function. They include clinical practice guidelines, guidelines for the application of preventive screening procedures, and guidelines for the ethical conduct of epidemiological practice and research. The EB Guidelines is a set of studies with a high level of evidence on a specific topic.

3. Economic Analysis: is a systematic approach to determining the optimum use of scarce resources, involving the comparison of two or more alternatives in achieving a specific objective under given assumptions and constraints. It takes into account the opportunity costs of resources employed and attempts to measure in monetary terms the private and social costs and benefits of a project for the community or economy (4).

4. Decisional analysis: is the application of explicit, quantitative methods that quantify

Table I. *Classification of best methodology for research question*

Research Question	Purpose	Best Methodology
Etiological Research	To determine whether a particular risk factor is correlated with the development of disease	• Prospective Cohort Studies • Case-Control Studies
Prognosis Research	To determine the outcomes of the disease in the population	• Prospective Cohort Studies
Diagnosis Research	To assess the accurancy, reliability and validity of new diagnostic and screening tests, compared to a gold standard in an appropriate population	• Cross-Sectional Studies
Therapy Research	To test effectiveness and efficiency of new treatments	• Randomized Controlled Trial

prognoses, treatment effects, and patient values in order to analyze a decision under conditions of uncertainty (4).

All research begins with a question derived from a general topic that piques your interest, often following reading, discussions, lectures, clinical experiences, etc.

There are four main "Questions of Clinical Research":

a. Etiology: to evaluate the risk factors of a disease;

b. Prognosis: to evaluate the natural history of the disease and its prognostic factors;

c. Diagnosis: to evaluate the accuracy of the tests;

d. Therapy: to evaluate the effectiveness of health interventions: prevention, treatment, care, rehabilitation etc.

Each type of study, according to its purpose and objectives, determines the appropriateness of the methodology applied. Consequently, less methodologically valid studies are used to generate hypotheses, and better structured studies are used to test them. The generation of an hypothesis and its subsequent development and validation are the real, critical progression in clinical medicine (Fig. 2).

The "Etiological Study" is performed to determine if a potential exposure to a particular agent may predispose a person to the development of a certain condition or disease. An example could be a trial that evaluates whether antomico-dependent morphological changes to the acromion can cause disorders of the rotator cuff.

"Prognosis Research" is conducted to describe the natural history of a disease or a specific medical condition or the results (clinical outcomes) that occur following specific treatment. An example could be a study that aims to determine whether small lesions of the rotator cuff can progress to larger lesions, such as massive ones. For this type of research, a

prospective cohort study is preferred. However, in some cases the prognosis of a disease can be studied using retrospective methods.

"Diagnosis Research" is aimed at demonstrating the validity and reproducibility of a new diagnostic test. An example might be the introduction of a semiological test to identify lesions of the upper lip of the glenoid labrum of the shoulder. For this kind of research, prospective cohort studies are generally used.

"Therapy Research" is generally applied to those studies which test the effectiveness (how an intervention works properly under ideal conditions) and efficiency (how an intervention works correctly in clinical practice) of drug, surgical or other treatment.

An example could be the use of one access pathway in minimally invasive hip surgery. The study chosen for this type of research would be a randomized controlled trial, which allows you to examine the effectiveness and efficiency of a given therapy.

The types of studies set out above, together with their objectives, are associated with a specific, well-defined study designs, which are be able to provide the strongest evidence and above all are the most practical and appropriate to achieve that evidence.

Prospective cohort studies or case-control studies are used in etiological research to determine the correlation between a particular risk factor and the development of a particular disease.

Prospective cohort studies are appropriate in prognosis research where we want to determine the outcomes of the disease in the population .

The Cross Sectional Study is the most suitable for diagnostic procedure research as they are designed to assess the reproducibility, reliability and validity of new and screening tests compared to a gold standard in an appropriate population.

For testing the effectiveness and efficiency of a new treatment, the best and only really suitable study, is the randomized controlled trial (9-10) (Tab. I).

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CHAPTER 3

GRADING OF EVIDENCE

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One of the pillars of EBM is that not all studies have the same weight, studies methodologically well done cannot be the sibling of an opinion, or of a single or sporadic case report. Hence the first authors began to draft study grading systems, publishing them in journals that adopted these systems as their own.

The Levels are essentially a heuristic, or short-cut to finding the likely best evidence. While ideally we should look at "all the evidence" that might help to answer a question, doing so is often impractical or unfeasible (1).

Sackett was the first to suggest a classification system in 1986 (2) and since then many of others have followed.

Over the years orthopedic surgeons too have increasingly based their clinical practice on evidence (3).

Today, the grading system is used in most papers to evaluate the scientific validity of a clinical study.

The hierarchical distribution of the work consists of Levels of Evidence which represent the primary source of evidence. Different levels of evidence should be identified for each clinical query, according to the methodological model adopted, this distinction allows us to make an accurate qualitative description of the methodological differences of each study (4-5) (Tab. I).

Randomized Controlled Trials (RCT) are defined as high quality although sometimes not statistically significant as long as they exhibit a narrow confidence interval. Poor quality randomized controlled trials are instead characterized by a follow-up of less than 80%, or by an improper randomization process.

The Systematic Reviews instead represent the combination of results of two or more main studies; the same results can then be more or less homogeneous.

High quality prospective studies are characterized by the fact that the recruitment of the patients starts at the same time, they begin before first diagnosis of the disease, and have a follow-up greater than or equal to 80%. Patients with specific characteristics are compared with others with different ones, at a given time.

Low quality prospective studies are characterized by the fact that patients are recruited at different stages of the disease and their follow-up is less than 80%.

Case-control studies examine two groups. One group includes patients, the "cases", who have been recruited to evaluate a specific factor, treatment or exposition to risk or protective factors; they are compared with another group called controls, who do not present these characteristics (for example patients with failed prosthetic surgery could be the "cases" while patients with successful prosthetic

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

Table I. *Grading of Evidence*

Research Question / Levels	Diagnostic Studies	Prognostic Studies	Therapeutic Studies	Decisional & Economic Analysis
I	• Systematic Review of 1st Level Studies	• HQ Prognostic Studies • 1° Level RCTs	• HQ RCTs • 1st Level RS	• Systematic Review of 1st Level Studies
II	• Systematic Review of 2nd Level Studies	• Restrospective Studies • Low Quality Prognostic Studies • 2nd Level RCTs	• Low Quality RCTs • Prospective studies • Systematic Review of 2nd Level Studies	• Systematic Review of 2nd Level Studies
III	• Systematic Review of 3th Level Studies	• Case-Control Studies	• Case-Control Studies • Systematic Review of 3th Level Studies	• Systematic Review of 3th Level Studies
IV	• Case-Control Studies	• Case Series • Case Report	• Case Series • Case Report	• Not Sensitive Analysis

surgery could be the controls). This is a retrospective study to find possible interactions between risk and prevention factors existing before the study.

Studies such as case series include patients who receive a specific treatment and there is no comparative group.

For diagnostic studies, first level of evidence is represented by studies that test diagnostic methods on consecutive patients, comparing them with a universally accepted gold standard of reference. Second, third and fourth level of evidence differ from first due to the lack of a consistent and well applied gold standard of reference.

Therefore, a well-conducted, randomized, double-blind, prospective follow-up study, with excellent results, offers strong evidence for the acquisition of knowledge in terms of diagnostic and therapeutic interventions.

All those methodological studies with an appropriate control group and which pay particular attention to the sources of error, should always be taken into account, especially when making changes to medical practice due to their ability to provide evidence.

So much so, as described in a recent systematic review, that the most read journals with a high impact factor were characterized by publications with I or II Level of Evidence (6).

Clinical research encompasses a wide range of scientific investigation including case reports on a single patient, case series, retrospective studies, prospective studies and multicenter randomized clinical trials. Understanding the importance of levels of evidence is important to avoid making the mistake of following low-level studies, as so often happens. Indeed most surgical practice today is based on lower levels of evidence (4) with less than 5% of orthopedic literature reporting randomized

trials (7).

Not always, at least in the past, have papers obtained the best from authors, in fact complete reports of allocation concealment, blinding in follow-up and surgical expertise were uncommon. Several problems in conducting RCT in surgery were reported.

These problems include a general lack of knowledge, the tendency to rigorously defend traditional procedures, the learning curve issue (seniority usually results in better outcome), the difficulty in blinding and ethical considerations. One solution to overcome known biases in surgical trial is expertise-based RCT.

Barriers that restrain the increase in the number of trials are the orthopedic surgeon's attitude, patient preferences and the availability of treatment outside trials. Challenges to conducting better quality trials include sample size, random allocation and blinding. Performing more high-quality trials could improve the evidence available for determining treatment effectiveness, thus resulting in better patient care (8-10).

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CHAPTER 4

EVIDENCE BASED PRACTICE

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Evidence Based Practice (EBP) studies the application of evidence derived from studies in literature to daily clinical practice, starting from some key questions such as: which would be the most effective treatment for this patient? Which tests would be best for this disease? What will be the course of this illness?

Therefore it is necessary to clarify at least the correct use of information, what is the architecture of the evidence and how to read critically and conscientiously such information. Today at least 30%-40% of patients do not receive care according to current scientific evidence, while 20% or more of the care provided is not needed or potentially harmful to patients (1).

The critical study of data in literature allows the best decision to be made concerning diagnosis and treatment and also allows the clinician to give the patient the correct information about the progress of the disease prognosis. A proper diagnostic and treatment plan should be accompanied the correct information to avoid unnecessary anxiety or false hopes.

The complete Evidence Base Medicine practice includes 5 steps:

Step 1: convert the need for information (etiology, diagnosis, prognosis, therapy) in applications where it is possible to give an answer.

Step 2: identify the evidence with which to answer these questions.

Step 3: critically evaluate the evidence according to their validity.

Step 4: integrate the critical evaluation with the surgeon's experience and the patient's characteristics.

Step 5: evaluate the efficiency and effectiveness of the first four steps.

Evidence Based Practice is not without difficulties due to its implementation; multiple factors concur and may include doctors, team practices, hospitals and the wider environment.

Cabana et al. (2) in a review of 76 studies showed not only the main problems encountered by clinicians but also why EBM guidelines were not used: lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of motivation and perception of external barriers beyond the control of the individual.

Therefore, it is necessary to clarify at least the correct use of the information, the architecture of the evidence and how to read the information critically and conscientiously .

1. Where to look?

The rapid development of practical resources necessary for obtaining evidence-based effectiveness has over the years led to a real hierarchy of access to such information. We therefore talk about a system called the "4s" (3).

Key words: Evidence Based Practice, interpretation, clinical practice

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In this system "original research" is at the base and the "synthesis" (systematic review like Cochrane Reviews) followed by "synopses" of studies and synthesis (very brief description of original and articles reviews) are placed above. Finally, the maximum level of evolution is achieved with the "information systems" (such as computerized decision support systems that link the individual patient's pertinent characteristics to the evidence). To this "4S" system, Haynes (4) himself has added a fifth "S": "summaries", this encompasses all the pertinent management options for a particular health condition (Fig. 1).

See Chapter 5 for an overview of the literature on EBM.

2. What to Look For?

Clinical trials and literature in all systematic researches begin with a question, the answer to that question should be based on the data available in literature. For example:

- Application of Research (Research Question): "What is the mortality rate at day 30 after surgery for knee replacement?"
- Question to be answered (Hypothesis Testing): "We hypothesize that older age is associated with a higher mortality rate at day 30 in patients who undergo knee replacement surgery, taking into account also their comorbidities ."

Formulating an hypothesis is essential as all studies are based on an experimental test of an hypothesis.

An hypothesis is structured properly if it is a summary of the research to be conducted, specifying the population to be studied, the nature of the control group, the statistical analysis to be performed to evaluate the results, and the strength and direction of anticipated changes between the study group and the control group.

In fact, the research question or hypothesis will determine the appropriateness of the methodology of the study and the analysis that will be conducted later.

3. How to assess the information?

The American Academy of Orthopaedic Surgeons (AAOS) has developed a model to evaluate the evidence of medical information according to the principles of EBM of a single scientific paper (5):

- Recording the quote: title, author and journal;
- Formulation of the research question or hypothesis: aim of the paper; analysis of the materials and methods: identification of the types of studies;
- Identification and enunciation of potential sources of errors;
- Description of the population to be included in the study;
- Statistical numbers: appropriateness of the tests and statistical errors;
- Results: estimated point of difference between the two groups, P value, statistical significance, power of search, size of the confidence limit, clinical significance of the difference.

Associate with each of these stages a full and complete formulation of the questions that underly the methodology and the quality of the studies is a good Evidence Based Practice praxis (Tab. I).

- Is there a control group in the study?
- Are there factors that the authors did not address when comparing the two groups?
- Have the authors set a gold standard for the diagnostic study?
- Is this a prospective or a randomized study?
- Are the populations examined similar ?
- How long is the follow-up period?
- Are there differences in outcome after treatment?

With the acquisition of this knowledge, medical information can be assigned to a specific level of evidence that takes into account the methodological

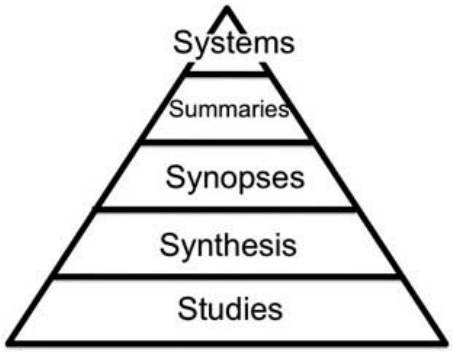

Fig. 1. *"5 S", hierarchy of services for finding current best evidence.*

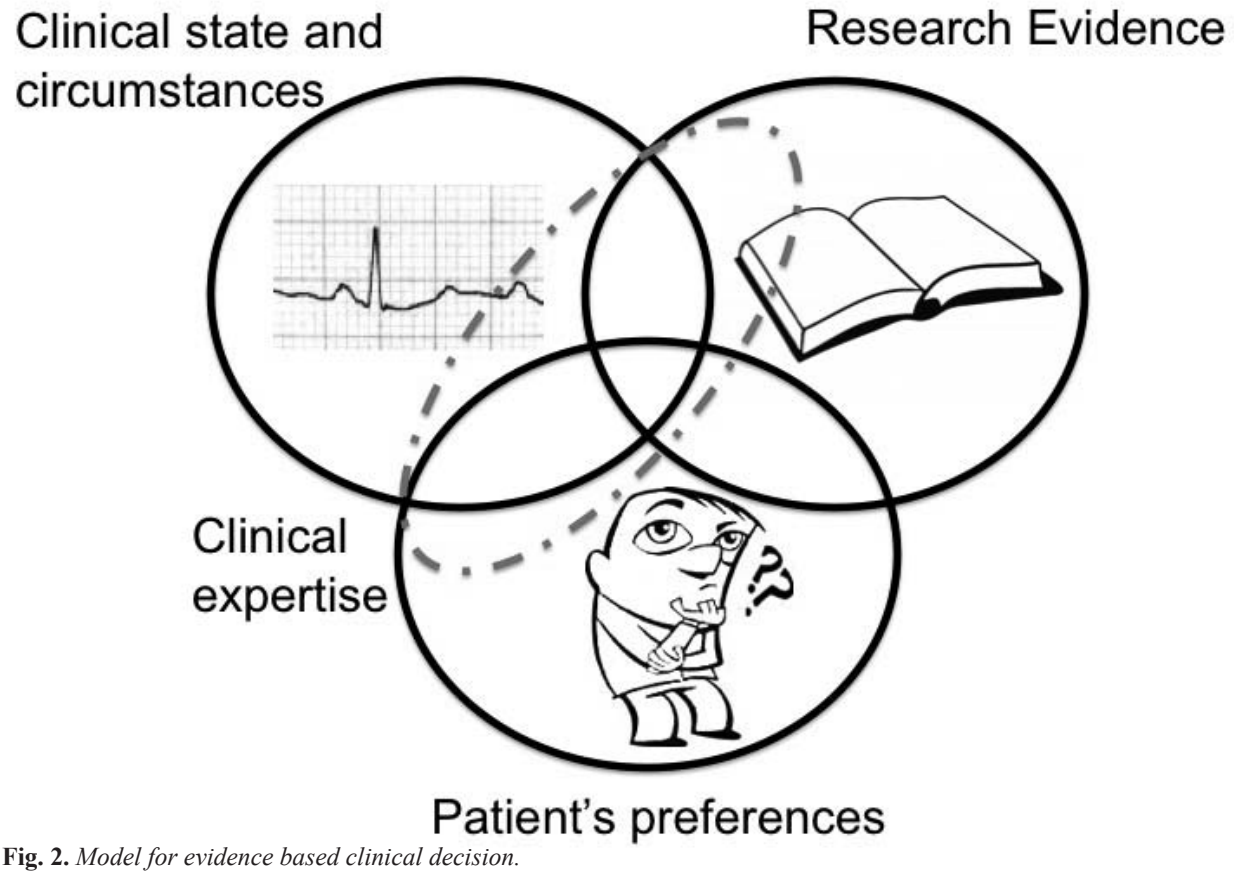

Fig. 2. *Model for evidence based clinical decision.*

quality of the study. The validity of the research must then be assessed to decide whether it is sufficient to be generalized in order to change a specific procedure in orthopedic practice.

In order to understand whether the evidence relating to a certain therapy is valid in the case of randomized trials, it is necessary to analyze some fundamental aspects:

1) Was the assignment of patients to treatment randomized?

2) Was randomization concealed to observers?

3) Were the groups similar at baseline?

4) Was the follow-up of patients sufficiently long and complete?

5) Were all the patients studied in the groups to which they had been randomized?

Randomization is not the only principle upon which to judge a clinical trial, it is necessary to examine its intrinsic methodology, how the initial research questions have been posed and finally whether it has been performed in accordance with the ethical principles of clinical research (Tab. II).

4. How to use evidence

It is imperative to remember that clinical decisions should not be based only on the extracted evidence: the role of the clinician should not and cannot shrink to a merely classifying and applying protocols. It is generally agreed that, as stated in an article by Haynes, "Evidence does not make Decisions, people do" (6). The patient's clinical and physical situation, disease evaluation and the treatment options available all equally contribute to making the final decision,

The next step is to evaluate the efficacy, effectiveness and efficiency of therapeutic/diagnostic

Table. I. *Clinical Study Appraisal*

Randomization	Were patients randomly assigned to treatment? Are the details given concerning the method of randomization sufficient to establish with reliability that randomization was conducted fairly for all patients? Was the allocation method such that it could be known by the patient and/or the investigator (the clinician) before the completion of randomization? Was randomization defined according to the comparability of treatment groups?
Blinding	Was the randomized treatment received by each patient adequately masked? Was the study conducted in double-blind? Was the clinical staff aware of which treatment group the patient was assigned to? Were patients unaware of which treatment they were receiving?
Follow-up	Were there randomized patients who did not receive treatment? Is it clearly specified how many patients have attended follow-up? How many patients were adherent to treatment? Have the reasons for non adherence to treatment been indicated?
Statistics	Was the primary objective clearly pre-specified and analyzed? Was the expected size of the study group discussed? Was the study concluded early or late compared to the specifications? Was an independent committee appointed to monitor data?
Results and Conclusions	Was an appropriate technique of analysis used ? Were total unadjusted data reported regarding the principle outcomes? Has a proper interpretation been given of the differences that were not statistically significant?

options with respect to these principles. So do not forget the patient's preferences, expectations, and compliance (Fig. 2) (7).

Evidence based medicine is therefore not a law to be followed blindly, but is the proper and fundamental starting point in order to make a clinical decision that must still be contextualized to the patient, the clinician's experience and circumstances.

The right way of applying the clinical implementation of EBP is not used enough; the barriers that hinder the application of evidence-based medicine must be sought not only in the behavior of health professionals but at other levels also. According to Grol and Weinsing (8) there are 6 levels on which barriers may lie and about which we must act in order to correctly apply the "theory" to "practice":

1) self innovation,

Table II. *Clincal Trial Appraisal*

Research Question	How many patients are needed for the study? What treatments should be compared? What is the comparable gold standard? How should the results be measured? Who would benefit from the results?
Feasible Answer	A sufficient number of patients must be enrolled Can statistical significance be achieved? Do the surgeons have the appropriate skills? Could the randomization method be affected by errors made by the examiners?
Ethics	Are patients free to refuse without any coercion? Are the controls ethically selected? Is any non-control treatment ethical? Will the study give a result which will be of benefit to the patients? Were refunds or other incentives offered to patients at recruitment? Were the surgeons in any way prejudiced about the effectiveness of treatment?

Table III

Level of Evidence	Implications for Clinicians	Studies needed
Level 1	Can be used in a wide variety of settings confident that it can improve patient care	At least 1 prospective validation and 1 impact analysis
Level 2	Can be used in various settings, may use predictions confident in their accuracy	At least 1 large prospective study demonstrates accuracy plus various smaller validated settings
Level 3	Can be used cautiously only in patients similar to patients in the study	At least 1 narrow prospective study
Level 4	Needs further evaluation before it can be applied clinically	Not validated or validated only in split samples with large retrospective database or by statistical techniques

2) the individual professional,
3) the patient,
4) the social context,
5) the organizational context
6) the economic context
7) the political context.

Clinical Decision Rule (CDR)

It is a practical aid to decision making; it assigns a different weight to the clinical information, the medical history and the laboratory results according to prognostic, diagnostic or therapeutic importance. Using a statistical analysis CDR shows the most powerful predictors and eliminates those that can be omitted without losing predictive power. It helps to control the factors that most affect the result of the clinical choice and, through assessments of efficacy, leads to a more appropriate decision. It is a useful instrument for clinical decision making when a case is complex or when we want to reduce costs without compromising patient care (9).

The CDR should not be confused with Clinical

Prediction Rules (CPR). CPR is an aid for clinicians to interpret clinical information, helping them to obtain the necessary data and suggesting the appropriate diagnostic and therapeutic regimen. Whereas CDR indicates the best possible treatment by providing diagnostic or prognostic scores using probabilities or a risk-stratification algorithm (10).

Some known examples of CDR are the Ottawa Ankle Rules - a set of signs and symptoms indicating a suspected fracture of the ankle following acute injury meaning that the patient may need an X-ray; the Pittsburgh Knee Rules - for suspected fractures after knee trauma; the APACHE II - a classification system for staging the clinical condition of a patient in the intensive care unit; the CHADS 2 - used for estimating the risk of stroke; the Ranson criteria - for predicting the severity of acute pancreatitis .

The drafting of a CDR must follow a rigid sequence of steps: firstly the factors with predictive power must be identified, these must then be validated to determine whether there is evidence of reproducible accuracy, and finally the effectiveness of the CDR in relation to cost/benefit must be verified. Depending on the degree of efficiency and reliability, CDRs can be divided into 4 stages: the first includes the rules that can be used in a wide variety of settings, the fourth includes the rules that need further evaluation before they can be applied clinically (9-10) (Tab. III).

The main problem of a CDR is its practical application, it is not easy to overcome the barriers of 6 levels described by Grol and Weinsing (8). There are different approaches used to overcome the barriers: by models relating to individual professionals or to interpersonal factors, system characteristic or models relating to tailoring strategies. Despite this they often fail to achieve satisfactory and evident results (8).

Evidence Based Medicine is not just a philosophical exercise, it is the attempt to extract evidence from clinical research. The ultimate goal of EBM is to be able to guide clinical practice towards the best modus operandi in order to obtain the best possible results (EBP).

In order to apply EBP to the practical reality of one's own practice/facility, the orthopedic surgeon must know, understand and judge evidence conscientiously, he should not just passively follow the rules but understand the reliability of what he reads, understand if and how it deviates from the patient he is examining and what benefits to expect.

EBM has been proposed as an alternative to what has been the rule in clinical practice to date: i.e. follow the lessons handed down by teachers based on the observation of a limited, albeit large, personal series. Applying EBM to clinical practice without understanding it and without the means to assess it is equivalent to listening to only one single teacher. EBM is not a religion with unavoidable dogmas, it is a set of instruments for transforming literature into clinical practice and cannot be separated from the caregiver's free will or personal interpretation.

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CHAPTER 5

EVIDENCE BASED MEDICINE RESOURCES IN LITERATURE

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Below is a list of sources for obtaining specific medical information on Evidence-Based Medicine:

Agency for Healthcare Research and Quality (AHRQ)

http://www.ahrq.gov/clinic

It is known as the Agency for Health Care Policy and Research (AHCPR)

Clinical Guidelines and Evidence Reports

It includes links of National Guideline Clearinghouse, plus Evidence Reports by AHRQ's Evidence-based Practice Center (EPC) and Preventive Service.

Bandolier

http://www.jr2.ox.ac.uk/bandolier

A synthesis of the considerations/dissertations on specific papers regarding the clinical practice of EBM.

Centre for Evidence Based Medicine (CEBM)

http://cebm.jr2.ox.ac.uk/

The Oxford University /Oxford Raddcliffe Hospital Clinical School Web Site includes links to the medical faculty's CEBM of, to the CAT database (Critically Appraised Topics), and links to evidence based medicine journals and material for EBM teaching.

Center for Research Support, TRIP Database

http://www.ceres.uwcm.ac.uk/frameset.cfm?section=trip

The TRIP database includes links to a wide collection of EBM materials including NCG, the Cochrane Library, the CAT bank and single papers.

Clinical Evidence, BMJ Publishing Group

http:www.clinicalevidence.org

The British Medical Journal's sources of Clinical Evidence represents a source for a continuous update on evidence and efficacy of care. It includes a list of update supports and describes the data obtained from evidence.

Cochrane Database of Systematic Reviews

http://www.cochrane.org

This is the systematic reviews of evidence periodically produced by the Cochrane Group. Reviewers discuss whether the data obtained are adequate to develop EBM based Guidelines.

Database of Abstracts of Reviews of Effectiveness (DARE)

http://agatha.york.ac.uk/darehp.htm

It contains abstracts written by reviewers from the University of York. They summarize both diagnostic and therapeutic revision papers and they discuss the clinical implications.

Effective Health Care

http://www.york.ac.uk/inst/crd/ehcb.htm

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Peer-reviewed newsletters about medical decisions. They are based on systematic reviews and a synthesis about the clinical effectiveness and acceptability of single therapies.

Evidence-Based Medicine

http://www.evidence-basedmedicine.com

A bimonthly publication which started up in 1955 by the BMJ Group. The articles summarize comments by clinical experts.

Evidence-Based Practice Newsletter (including JFP Patient-Oriented Evidence that Matters)

http://www.ebponline.net

InfoPOEMs

http://www.infopoems.com

Institute for Clinical Systems Improvement (ICSI)

http://www.ICSI.org

A non-profit independent collaboration that develops Guide Lines.

National Guideline Clearinghouse (NGC)

http://www.guidelines.gov/index.asp

A guideline database of clinical practice that aims at comparing different guide lines regarding methods, purposes, outcomes and primary recommendations.

National Health Service (NHS) Centre for Reviews and Dissemination (CRD) http://www.york.ac.uk/inst/crd/.

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CHAPTER 6

CRITICISMS AND LIMITATIONS

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Since its inception Evidence Based Medicine has been frequently criticized and its limitations underlined.

Many of the criticisms made are based on a lack of knowledge about methodology and the prejudices formed over time.

Sharon (1) has examined the major misperception surrounding EBM: it denigrates clinical expertise, ignores patient's values and preferences, promotes a cookbook approach to medicine, it is simply a cost-cutting tool, it is an "ivory tower" concept, it is limited to clinical research, it leads to therapeutic nihilism in the absence of evidence from randomized trials.

All these doubts easily fall by analyzing the definition of Evidence Based Medicine: "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (2). The implementation of EBM occurs at different times: first it converts the information arising in clinical-practice in to questions which appear to have an answer. It then gathers the best available evidence to answer the questions and critically evaluates the quality of the 'qualifying' evidence for validity. This followed by the important step which combines practice and theory, the integration of evidence with the medical personnel's clinical experience and the patient's wishes. Finally each outcome must to be evaluated to understand its effectiveness and eventually correct errors.

It is therefore incorrect to state that EBM does not take into account the experience of the clinician nor the opinion of the patient, or that it offers "cookbook medicine" (3-4). EBM offers and conscientiously analyses the information available in literature, weighing it up and making it available to both clinician and patient so they can make the best choice. Even the insinuation that EBM is only a way to cut costs and standardize treatment is a criticism that does not take into account the fact that all EBM research is indifferent to costs and that its aim is to improve the patient's quality of life which may actually lead to a rise in of healthcare costs: If a particular treatment regimen or screening test is effective, it will remain so despite its cost.

One outstanding example is the treatment in orthopedic surgery with Low Molecular Weight Heparin compared to treatment with heparin alone or heparin + Dihydroegotamine or Dextran. It is much more expensive but very effective and easy to use at home too, so it is prescribed on a broad scale (5).

The concept of the "ivory tower" is based on the distance between the philosophical thinking of intellectuals and the real world with its problems. It is a superficial concept where EBM is concerned, but if its principles are examined in depth it will become obvious that EBM is exactly the opposite. In fact

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it focuses on practical problems and their analysis which leads healthcare givers to questioning and asking themselves how they can improve clinical practice. In fact, the main goal of EBM is just to update clinicians on the best evidence available for their daily activities, in a comprehensive and fast manner (6).

Many believe that only RCTs, RS and meta-analyses can provide evidence and, therefore, in those fields where these sort of studies have not been performed, no evidence is available and clinicians been left in the so-called gray area regarding their decision making. This is very much so in Orthopedics where the RCTs in literature are few due to the fact that treatment in orthopedics is mainly surgical making randomization difficult. Where RCTs have been performed, the study population is small.

Indeed the purpose of EBM is to find the best available evidence existing to answer a specific question, and it is said that not only RCTs and meta-analyses are the sources of evidence, although they are at the top of the pyramid of evidence for treatment decisions.

Also as previously mentioned, the RCT is the best type of study to answer questions concerning treatment, but they certainly are not for matters related to diagnosis, prognosis or etiology for which the best available evidence includes not only level I studies but any study that currently exists on the specific topic.

Some authors instead have emphasized limitations that go far beyond the misperception of EBM (7). The main limitation that many see in EBM is the poor philosophy of that discipline based only on the empiricism. This is an epistemological criticism that not so much involves the practical question, but rather the very philosophy behind EBM.

The main criticism arises from the idea that this is an approach based on empirical evidence from experimental studies designed only to minimize BIAS rather than being based on a solid physiological theory, with the presumption that scientific observation is independent from the experiment, without assuming that observers are "biased" themselves, and that prejudice is impossible to eliminate observer (8).

Furthermore, the possible applications are limited to observations, and observations in turn limit the theories: the clearer the observations, the more theories are challenged and possibly replaced by others: more specific are the questions, more careful are the observations and ultimately more useful. So the observer affects the theory and the theory influences the observer. EBM due to its quantitative nature ignores this interaction assuming that the observer is objective and refuses this bias. This type of paradigm, based entirely on empirical data, is seen as ''a conceptual box which scientists try to fit into nature'' (9) stated incorrectly that EBM medicine is totally submissive to empiricism.

As matter of fact EBM does not look only at the empirical process. An RCT that proves a theory with no scientific basis is of very little value. The impact an RCT can have on clinical practice is greater, the greater its physiological or pathophysiological basis (10). EBM is only a tool for the clinician to improve his practice, it is not a substitute for physiological or pathophysiological concepts, which remain at the base of knowledge of every medical practice.

A criticism which is difficult if not impossible to argue is that there is no evidence, according to the criteria of EBM themselves, of how this has an effect on decisions made in clinical practice. There is no evidence that patient care based on statistically significant clinical studies are better than treatment based on qualitative data or exclusively on the clinician's experience.

Obviously, given the resources, in terms of costs and time, spent by clinicians studying EBM and on trials, the practice of EBM should be considered as an intervention in clinical practice and therefore its effectiveness should be analytically tested.

However it is undeniable that EBM is based on scientific method, and that it promote new and better methods for preventing, detecting and treating diseases more than was thought possible over the last century.

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