

EVIDENCE-BASED MEDICINE

*“THE GOOD, THE NOT SO GOOD AND THE BAD”*

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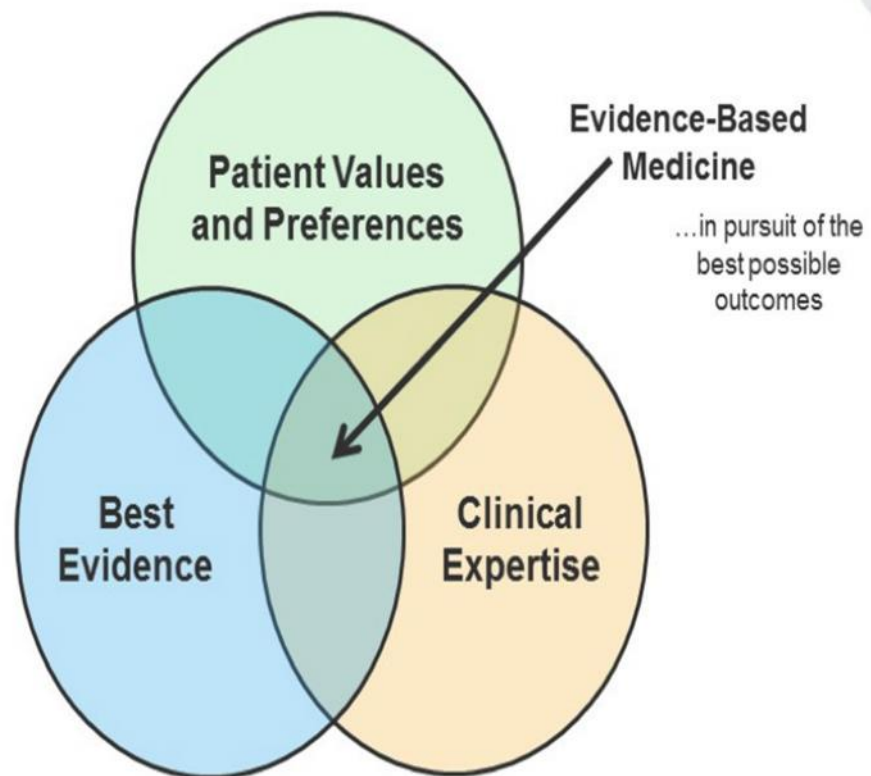
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## INTRODUCTION

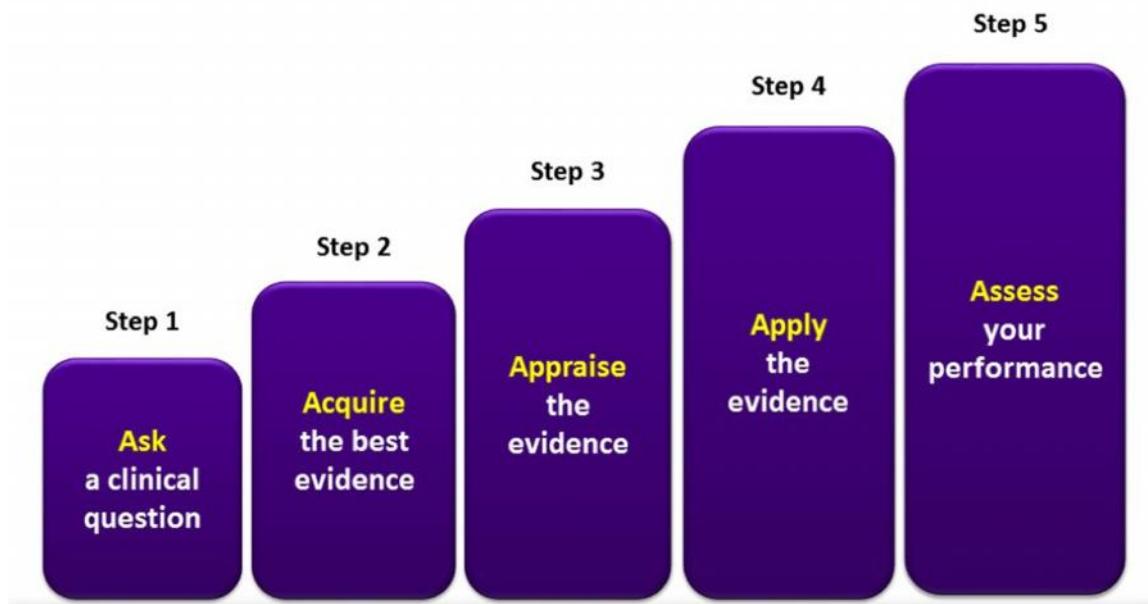
The definition for evidence-based medicine (EBM) varies and is continually evolving, but one of the best is as follows: “EBM is defined as the integration of the best available evidence with our clinical expertise and our patients’ unique values and circumstances” [1]. The image below provides a graphical representation of this concept.

## Components of Evidence-Based Medicine



EBM involves the following 5 step approach (The 5 A's) as illustrated by the figure below:

## The 5 Steps of Evidence-Based Medicine



1. Asking an answerable clinical question using PICO. PICO is commonly used acronym for forming clinical questions when using EBM [2].
  - P = Patient or problem
  - I = Intervention
  - C = Comparison intervention
  - O = Outcome

An example of a PICO question would be: A 62-year old male with a history of non-insulin dependent diabetes is taking Metformin. Does Metformin compared to Actos improve his condition as measured by lowering his Hemoglobin A1C?

2. Acquire the best evidence. Finding the evidence to an answerable clinical question can be time consuming and challenging. There are several databases to search in order to find published clinical studies.

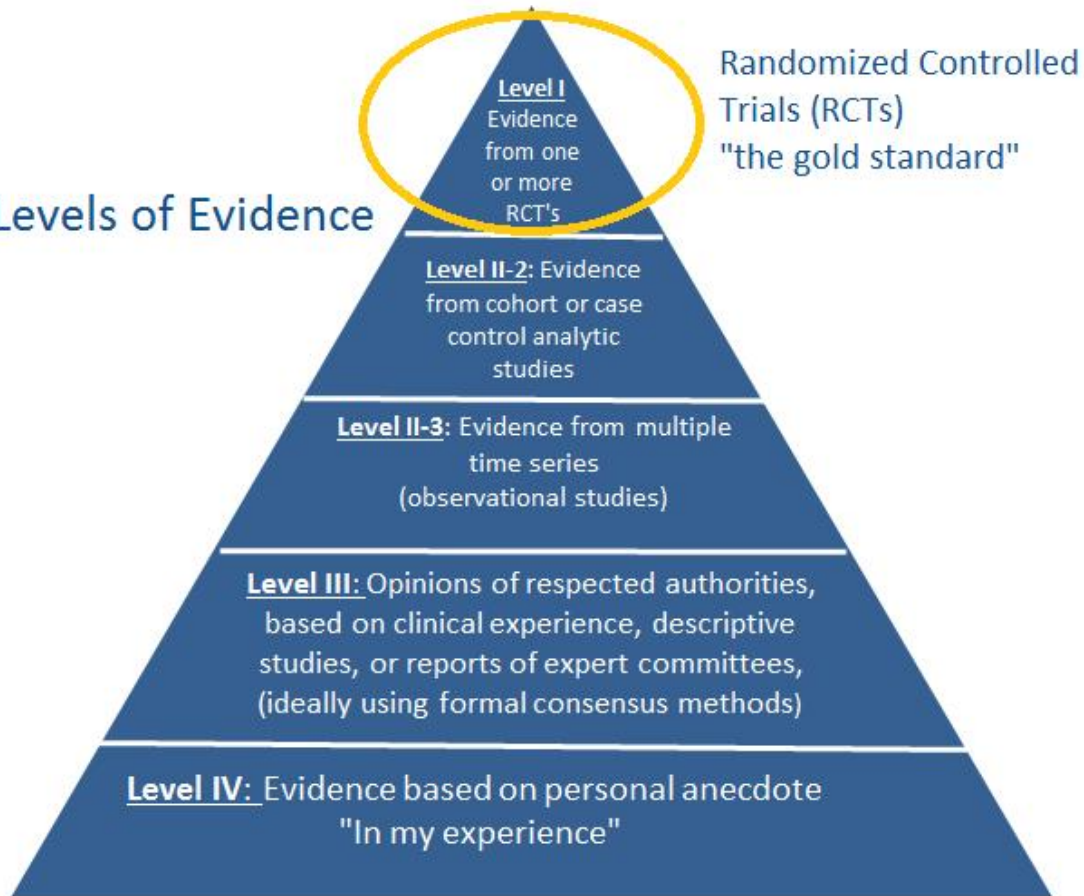
Three very highly regarded and popular databases are The Cochrane Library, PubMed and Embase. There are many types of studies which include expert opinion, case series/case reports, case-control studies, cohort studies, randomized controlled trials and systematic reviews.

3. Appraising the evidence. There are three key questions to ask when looking at a study reported in the literature.
  - Is the study valid and relevant?
  - What were the results of the study?
  - Will the results help in treating the patient?
  
4. Apply the evidence. Once all of the relevant and up-to-date evidence has been examined, it must be integrated with the clinical opinion of the medical provider as well as the patient's values and circumstances. The evidence should be explained to the patient as well as the risks versus benefits. There should be shared decision-making with regards to acting upon the evidence.
  
5. Assess your performance. It is important to assess at frequent intervals as to whether or not any of the four steps discussed above need to be improved upon. Formal auditing of performance may be necessary to determine if the EBM approach is improving patient care and outcomes.

#### EVALUATING THE LEVELS OF EVIDENCE

It is important to understand the levels of evidence when evaluating a clinical topic. In the scientific and health care community, it is widely accepted that there are four levels of evidence (see figure below). Since the introduction of levels of evidence, many organizations have modified the classification of levels (some have added subsets for the different levels). However, though there may be certain subtleties of the levels, the overall categories are the same.

## Levels of Evidence



- Level I – Evidence in Level I is considered to be the gold standard of medical knowledge. It comes from randomized, double-blind, placebo controlled trials (RCTs). Randomization in a clinical trial helps to remove bias and to ensure that the two groups being compared are truly similar.
- Level II – Evidence in Level II is not considered to be quite as reliable as evidence from Level I; however, it is still considered to be better than Level III and Level IV. Level II evidence comes from three different sources:
  - Controlled trials without randomization
  - Cohort or case-control analytic studies

- Multiple time series studies (RCTs cover only 10% - 40% of what clinicians do. It is often true that the best evidence available to clinicians is their own observed aggregate data.)
- Level III – Evidence in Level III is based upon expert opinion from those who have narrowed their focus as much as possible about a complex area. The downside is that sampled sizes are generally small and there are not any control groups. This can lead to a large margin of error unless group statistical techniques are used to compile the opinions of an appropriate number of experts.
- Level IV – Evidence in Level IV is based upon personal experience. This is the least desirable source of evidence and lacks any statistical validity.

#### EBM – THE GOOD

EBM helps clinicians leverage the available evidence to make the best decisions for patient care. There is a vast amount of scientific knowledge that is being published annually, and it is difficult for a clinician to keep abreast of the latest medical advances and best medical practices. EBM helps to bring forth the “shortlist” of the best available evidence. Without EBM, it has been estimated that a primary care physician would need to read 17 journal articles daily 365 days per year. This is a virtually impossible for a clinician to do.

The existence of the EBM body of knowledge allows a clinician to easily search large online databases and determine what the standardized guidelines are for treating a certain condition. Also, electronic health records (EHR) that integrate EBM protocols can prompt the clinician to order certain laboratory tests as well as make medication suggestions for a certain health condition. Thus, EBM protocols offer a way for a clinician to stay current by using standardized guidelines.

Further, EBM approaches have been found to be beneficial in specific clinical conditions. For example, it has resulted in better postsurgical recovery times, improvement of stroke and myocardial infarction aftercare and safer ways to deliver breech babies. Implementing EBM provides a framework for a systematic approach to caring for patients, and in many cases patient outcomes are greatly improved.

#### EBM – THE NOT SO GOOD

EBM was not intended to be a cookbook approach to patient care. However, many times clinicians use EBM guidelines to the detriment of the patient. They can become complacent in their clinical approach and feel they if they follow the EBM guidelines, they are doing the right thing. Using this simplified pathway, they fail to adhere to integrating clinical expertise which is part of definition of EBM.

There are other risks to using an EBM approach. For example, if a clinician searches the literature looking for the evidence to answer a clinical question, the perfect evidence (RCTs) may not be available. This can cause what some would entitle “evidence paralysis”. It is important for the clinician to understand that sometimes it is necessary to use the best evidence that is available at any given time, even if that evidence is at level III or IV on the evidence hierarchy.

A potential downfall to using EBM-based approaches is the risk of knee-jerk changes to the clinical paradigm as new studies literally come out daily. Practitioners must remember that new studies do not automatically “override” older studies that may have been more credibly performed. The recent controversy surrounding testosterone administration is a perfect example. The new study, actually a retrospective observational study fraught with multiple compounding biases arrived in JAMA, indicated that testosterone administration increased the risk of heart disease in men. All of the prior RCTs and other studies showed either no impact on heart disease or a favorable impact. However, due to the inherent biases in the

system (*hint: Big Pharma does not make excess profits from testosterone*), the JAMA article caused an immediate change in the clinical paradigms of many practitioners. The bottom line is that it is very important for the clinician to be very discerning when evaluating the literature and to be very deliberate when completely changing clinical paradigms. Clinicians have to remember that not every study is a valid study.

An additional not so good outcome to an EBM approach is that in certain clinical environments, clinicians are reprimanded and chastised by insurance companies, peers, hospital administration and others for deviating from the EBM guidelines. We have to remember that EBM forms an evidence base that we can broadly call a guideline, but guidelines are not applicable for every clinical situation. Forcing a clinician to adhere to this approach challenges the very foundation of the definition of what EBM was intended to be.

Not so good outcomes can also occur when a provider or practitioner ignores the duration of the study. It is not uncommon for a study to be represented as though it was a long-term study, when in fact most studies cover a limited duration of time such as 2 years or 5 years. For example, consider the use of EBM in organ donor situations - specifically kidney donors. In this real-life example, a prospective donor was advised repeatedly by the medical establishment that there were no “downsides” to donating a kidney. He was advised that the rate of renal failure was the same in patients who had both kidneys and patients who had donated one kidney. What he was not told is that the study supporting that outcome was only based on 2 years of data because hospitals only follow donors for 2 years after a donation [3]. He later discovered a study that looked at the long-term risks for kidney donors, and discovered that they had an increased risk for developing end-stage renal disease, renal carcinoma and an increased risk for cardiovascular disease. Had he known this information, he stated that he would not have made the decision to be a kidney donor.



Notwithstanding the good and honorable intentions of EBM, the problem is that much of the “evidence” that forms the backbone for EBM has been severely compromised by biased funding sources, pharmaceutical companies and special interest groups. In fact, Dr. John Ioannidis, professor of medicine at Stanford University and Director for the Stanford Prevention Research Center argues that EBM has been “hijacked” [4]. Today, it is way too obvious that EBM has been compromised. Consider the following examples:

1. EBM today supports the administration of statin drugs when a patient’s total cholesterol is over 200. The reality is that there is no credible evidence that total cholesterol is a valid predictor of atherosclerosis, and there is very little evidence that they do any good except in certain limited cases. However, the pharmaceutical industry generates 30-40 billion dollars per year revenue selling these drugs that are supported by “EBM”.
2. In the case of ductal carcinoma in situ (D.C.I.S.) Stage 0 of the breast, an EBM approach has been to perform a lumpectomy, mastectomy or double mastectomy. Recent studies show, however, that women with D.C.I.S. Stage 0 who had this treatment had close to the same mortality rate for breast cancer as women in the general population [5]. It appears that many of these women had unnecessary surgeries. Dr. Otis W. Brawley, chief medical officer at the American Cancer Society stated that, “In medicine, we have a tendency to get too enthusiastic about a technique and overuse it. This has happened with the treatment of D.C.I.S.”

3. Thyroid cancer treatment is moving in a similar direction as D.C.I.S Stage 0. With the increasing use of ultrasound-guided needle biopsy of thyroid nodules, many patients have been diagnosed with papillary carcinoma of the thyroid. The EBM approach to treating papillary carcinoma has been complete thyroidectomy and radiation. Papillary carcinoma is a relatively benign tumor with an excellent prognosis. The terminology of classifying papillary thyroid carcinoma as a cancer has caused aggressive treatment that is usually out of proportion to the actual pathology. An international panel of doctors has officially downgraded this condition and has stated that this type of tumor is not a cancer at all [6]. They have renamed papillary carcinoma of the thyroid as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). This change is estimated to impact 10,000 of the nearly 65,000 thyroid cancer patients a year in the United States. Major medical centers have already begun treating these patients less aggressively; however, thyroid experts predict that this will not be the norm in the rest of the country and the rest of the world. For now, many patients will continue to have unnecessary and potentially harmful procedures when in fact they really do not have cancer.

Clearly, these examples show that EBM has been compromised. Now let's understand how this happens. Given that most studies are funded by the pharmaceutical industry, this presents a serious problem for the overall evidence base. Clinical decisions based on such evidence are likely to be misinformed leading to patients being given less effective, more harmful and more costly treatments. It is clear that EBM urgently needs more investment in independent research. EBM desperately needs independent bodies, informed democratically to set research priorities, participate in study design and study outputs.

Consider the following reference documenting the impact of bias. Although industry influence has been pervasive across medicine, psychiatry has been

at the epicenter of much of the controversy about funding source bias and conflict of interest. Among randomized, double-blind, placebo-controlled studies in psychiatric journals, those that reported conflict of interest were five times more likely to report positive results. [7]

Also, consider the following case where direct manipulation was shown. In 2012 GlaxoSmithKline (GSK) was fined a record \$3 billion for multiple criminal and civil offences including the unlawful promotion of medicines, failure to report safety data and false reporting. [8]

#### SHOEMAKER CIRS PROTOCOL – A MAJOR ADVANCE IN THE UNDERSTANDING, DIAGNOSIS AND TREATMENT OF CIRS

The body of knowledge supporting Dr. Shoemaker’s CIRS protocol includes works that meet the criteria for Level 1 RCT “gold standard” as well as works that meet the Level II and Level III criteria. The approach to data collection is disciplined. The development of the diagnostic protocols is creative and supported by solid science. For example, NeuroQuant provides a highly-unique fingerprint that can be used to support a CIRS diagnosis. The outcomes are measured not only in clinical terms but objectively by normalization of key lab values (i.e. VCS, C4a, MMP-9, and MSH) that were previously outside of the expected range. In short, the diagnostic and treatment protocols represent a major advance that is supported by a growing body of evidence that is being proven every day through application by the practitioner base. People are being properly diagnosed and they are being healed. That is the ultimate evidence and the ultimate goal of EBM. The point here is that in emerging areas, applicable evidence may exist at all levels and this evidence should be considered.

#### SUMMARY

There is no doubt that EBM is needed and that the intent of EBM is to ensure some level of consistency and application of the best possible treatments that are supported by the evidence. But it is also clear that the current system is severely compromised and fails to support treatments

that are not supported by the multi-billion dollar pharmaceutical companies and other wealthy interest groups. The time and cost to run a Level I high-quality RCT, double blind, placebo controlled study with a large number of participants is beyond the reach of smaller organizations that are trying to bring viable solutions to patients that need them.

Further, even when intentions are good, we desperately need to improve the reliability of study outcomes by adding the presence of formalized unbiased third parties that participate in study design, study execution and study outputs. Other industries including the Information Technology industry use third parties such as CMMI (Capability Maturity Model Integration) Appraisers to assess the process maturity of organizations that develop software. In the healthcare industry, compounding pharmacies that are 503(b) registered have to use independent third parties to assay each batch of sterile products that they produce. The bottom line is that there are numerous examples of using third parties to provide a higher level of certainty about the outputs, and this approach is needed in EBM.

So, while we may continue to consider the Level I RCT to be the “gold standard”, hopefully this paper has shed some light on the reasons why the Level I RCT cannot always be relied upon as the best basis for clinical decision-making. Practitioners need to be aware of study bias and other factors that may make some of the evidence unreliable. In this light, I believe that it is necessary to broaden our thinking and give substantial credence to Level II, III and even level IV evidence when the potential benefits outweighs the risks.

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