

REVISITING THE EVIDENCE – BASED MEDICINE PARADIGM – THE NEED TO BE AWARE OF ITS LIMITATIONS. A QUICK OVERVIEW AND A BRIEF REVIEW OF SOME RECENT CRITIQUES

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Since its inception two decades ago the evidence based medicine (EBM) became the dominant paradigm in medical thinking. Its widespread dominance is often taken uncritically by the clinicians who conduct their practice following its lines. The need for a more critical view became indispensable in the last years after a variety of critiques that disclosed the limitation of the EBM conception. The aim of this paper is to present some of the main critiques that expose the conception’s limitations and emphasize the need for a more conscientious take on the approach.

Keywords: evidence based medicine, critiques.

EBM is an influential orientation that dominated the medical practice in the last two decades. From its official inception at the beginning of the 90s till now its influence grew constantly and its ideas spread worldwide seeming to become the state of art of doing medicine at the beginning of the XIXth century. Today we have a great number of institutions, organizations, congresses, journals and a steady flow of guidelines and books promoting and implementing the EBM view. Among the well-known hotspots for EBM we could mention such prime choices as the Oxford Center for EBM (OCEBM), The Cochrane Collaboration, US Preventive Services Task Force, CONSORT (Consolidated Standards of Reporting Trials) etc. The influence could be also seen in the spread of the its intuitive denomination to other areas more or less related to the original movement. So one can find today in circulation such expressions as evidence-based policy, evidence-based public health, evidence-based health care, evidence-based decision, evidence-based management that draw basically on the same thinking paradigm.

The aim of this paper is twofold: in a first move we will briefly review the major ideas of this orientation in order to be able in the second move

to discuss the main points of criticism raised against this view by the medical specialists but also by philosophers of science. The discussion of such points are important in order to realize the limits and extend of this conception and to rise the awareness of the hidden dangers when engaging in its practice.

INTRODUCING EBM

Much of the popularity of the movement is due also to its suggestive denomination which captures in an intuitive way its essence and became over time almost a slogan. The name nevertheless contains its inherent fuzziness. Each of the three terms of the expression evidence-based medicine of the conception could be seen as complex and problematic. A disambiguation attempt will inevitably lead to a narrowing down of the domain of EBM as Thompson showed¹.

The importance of the conception lies clearly on the third term. The different issues that appear could be revealed also in the ways the denomination is translated in other languages. As for example, in French, we get the following

¹ Thompson in his 2010 paper “Causality, mathematical models and statistical association: dismantling evidence-based medicine”.

variants: médecine basée/fondée (alternative that points also to other inherent ambiguities) sur des données probantes/admises, sur des éléments probants, sur le niveau de preuve, sur des/les faits, sur des faits prouvés, sur des preuves, sur la preuve, sur le niveau de preuve et sur l'expérience clinique. This variety of options is not a linguistic issue but points to the more complex way in which evidence is understood by EBM and its role in clinical practice, as it will become more clear in the following paragraphs.

A nonconformist and refreshing starting point for an understanding of what EBM might be is to force the logical limits and ask (not without irony) as some authors did² – on what was medicine and medical practice based before the EBM showed up? This points to the fact that there is indeed something to be distinguished and stressed here in relation to the evidence as referred and conceived in EBM. The view is built in contradistinction to some older way of understanding medicine and medical practices ultimately boiling down to the issue of evidence.

Looking back historically, a more generous perspective might distinguish a kind of oscillation between two fundamental ways of doing medicine and understanding its practice – a rationalist and an empiricist way.³ For the first way the emphasis falls on the knowledge of the mechanism of disease, of the theory that explains the mechanism that generated that disease. The last one is characterized by a more pragmatic attitude focusing the main interest on whatever works in a situation in order to achieve the healing and being less interested in the theory or mechanism behind. EBM belongs to this last group.

As an early precursor of the actual EBM conception one might recognize the XIXth century French physician Jules Gavarret, who in his work *Principes Généraux de Statistique Médicale* (1840) argues for the fact that judgments of the efficacy of a treatment should be made only on the basis of observation of its effects in large numbers of individuals (the Law of Large Numbers). Nevertheless, this call remained isolated and ignored for over a hundred years. Especially in the

context the medical practices in the first part of the XXth century when the focus moves on the rationalist way of doing medicine as for example the influential Flexner Report in USA argues in 1910 for the need of a heavier emphasis on basic sciences in medical practices.

Later in the XXth century, the accumulating advances in epidemiological research in the second half of the century and the introduction of clinical trials practices in medicine, paved the way to the emergence of the EBM paradigm. The explicit formulation is due to a group at McMaster University in Canada in 1992.

In the following paragraphs I'll try to unpack the conception by discussing the major features of the EBM view. As already mentioned, there must be an opposition to some older view. This older view is the one that is based on knowledge of the clinician and the decision is based on his/her clinical experience. In their manifesto the founders explicitly state that the “old way” of doing medicine is characterized by appeal to authorities higher in the medical hierarchy involving an appeal to unsystematic observations from clinical experience adding to knowledge provided by the basic sciences which describe the disease mechanisms and the pathophysiology, and the additional evaluation of the new treatments using “a combination of traditional medical training and common sense”. Meanwhile the new way of medical thinking (the one of EBM) adds something important to the older view: it requests the clinicians to be permanently informed with the up-to-date information from the medical literature – esp. the one presenting the results of clinical trials, systematic reviews and meta-analyses, as we will see. It's not by pure chance that one of the major recent textbooks on EBM bears the title *How to read a paper*⁴. This request calls in consequence for the development of a third skill – one that involves the ability of proper interpretation of the latest results. Here lies, as we will, see one of the major difficulties of making the EBM view more accessible to medical practitioners.

If we look to some official definitions of EBM, a general, well-known one states that EBM is “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of

² Howick explicitly does in his 2011 book *The Philosophy of Evidence-Based Medicine*.

³ As suggested by Newton in his paper “Rationalism and Empiricism in Modern Medicine”.

⁴ Written by Trisha Greenhalgh and published in 2010.

individual patients”⁵. But this does not give us any insight into its specific nature and the specificity of its methods. A more explicit definition draws attention exactly on its very distinct feature “the use of mathematical estimates of the risk of benefit and harm, derived from high-quality research on population samples, to inform clinical decision-making in the diagnosis, investigation or management of individual patients”⁶. We could now see that the specificity of the evidence in EBM is given through the special way evidence is gathered and valued. Epidemiological measures play a central role and this makes out also one of the major difficulties of making it more popular and easy to understand by the clinicians.

Nevertheless not all epidemiological evidence is equal. Different methods of getting such evidence are ranked and placed in strict hierarchies. Evidence from other sources is also incorporated in such hierarchies and so the entire evidence is ordered, ranked and rated according to its quality. These hierarchies aim to provide the clinicians a way on which they can base their decisions by making reference to on the strongest evidence available in a situation.

The idea of hierarchy of evidence is actually central to this conception. David Sackett originally proposed the idea of ranking evidence on a scale as an objective method for resolving disputes amongst physicians at consensus conferences. Over the time a multitude of hierarchies and categorization schemas were advanced and used in different ways. The hierarchies depend on the type of clinical questions being asked specific to treatment studies, studies of prognosis, or studies testing the utility of clinical decision rules. There is also variation depending on the groups that propose and develop the hierarchy.

In 2002 AHRQ reported forty systems of rating in use, six of them within its own network. This is somehow ironical for a conception that had as initial goal to set a unified standard of for medical decision making. It became therefore necessary to synthesize and compare these hierarchies. Starting in 2000 the GRADE Working Group – an informal collaboration group – set as its goal to reach consensus on one

system of rating the quality and strength of evidence claiming that “Our aim is to develop a common, sensible approach to grading quality of evidence and strength of recommendation”⁷.

Despite the variety of the particular schemas one might find a general pattern underlying all of them. This pattern will place randomized studies at the highest level, nonrandomized studies in the middle and on the bottom level such classical evidence as: bench research, physiologic principles or anecdotal evidence. One can see how these are implemented by two of the most influential hierarchies containing the ranking and description of each level of evidence: the U.S. Preventive Services Task Force (USPSTF) and Oxford CEBM Levels of Evidence (UK). Here are the levels of evidence as presented by U.S. Preventive Services Task Force (USPSTF):

Level I: Evidence obtained from at least one properly designed RCT

Level II-1: Evidence obtained from well-designed CT without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series designs with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

The OCEBM also provides such a hierarchization categorized on the different questions that are oriented towards different aims (not detailed in the below schema) such as diagnosis, prognosis, screening treatment, harms or benefits. A general view is provided below⁸.

As one might notice the highest level of evidence we find the randomized controlled trials.

Systematic reviews that constitute a thorough search of the literature and an evaluation and grading of clinical trials appear as the optimal way to report such findings. Another way is given through meta-analyses – studies that integrate the actual data from different but similar high-quality trials to give an overall single statistical result.

⁵ Sackett D.L., & al “Evidence based medicine: what it is and what it isn’t”.

⁶ Greenhalgh, Trisha (2010). *How to Read a Paper: The Basics of Evidence-Based Medicine*.

⁷ <http://www.gradeworkinggroup.org/FAQ/index.htm>

⁸ <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>

Table 1
Levels in the hierarchy as provided by OCEBM

Level of Evidence	Method
1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT)
2c	'Outcomes' Research
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or 'first principles'

FROM A CRITICAL POINT OF VIEW

In this section I will turn to the criticisms that were fired at the conception exposing this way its most sensible parts. These have to be taken into consideration by anyone that engages the view using its ideas as guiding lines in his/her practice

I will start by referring first of all to the general and most common accusation voiced by the adherents of the older view: an accusation that points to the unreasonable move of the EBM conception of getting rid or rather sub-evaluating the knowledge of the specialists and of the personal expertise of the clinicians. The accusation is that the EBM view forces the clinical decision to be based on information from outside the clinical practice and clinical experience by emphasizing the importance of orienting the clinical decision after the guidelines and statistical studies. EBM-driven medicine is therefore a sort of cookbook medicine (as the accusation can go) that neglects the intuition and the personal experience of the clinician, the interaction between clinician and the patient but also the patient values etc. It overlooks the "art of medicine", the unregimented nature of medical practice, by forcing it instead to get into a rigorous technique without contact to the real humans engaged in the medical action. It threatens the autonomy of the physicians by putting clinical decision-making in the hands of "Infostats technicians" (epidemiologists, statisticians etc) and imposes this way a new form of authority alien of the medical practice.

Despite the intuitive appeal (esp. for the practitioner) of such sort of accusations, one might admit that they are only partly objectively justified. The argumentation has to be broken down into

more detailed and specific ways, as we will see, diverging on various issues from ones of ethical sort to others concerning the need to reconsider the priority of other sources of evidence. The reaction that seems straight concerns the neglect of patient values, the overlook of the personal aspects and of the individuality of the case. In terms of kinds of evidence that might be put in the way one neglects the narrative evidence that builds up in the personal interaction patient-medical specialist. In general, the new developments in EBM search to accommodate the above mentioned issues and to propose solution to these concerns.

But the major critiques were triggered by the specific view on evidence that the conception assumes the way evidence is ranked, compared and valued. The idea of the hierarchy of evidence becomes central as Montori and Guyatt also mention⁹, the "first fundamental principle" of EBM is the hierarchy of research evidence. The critical positions vary in their scope from radical ones denouncing the danger of using such hierarchies calling for their rejection to other moderate positions that denounce the rigidity of hierarchies or their absolute validity and deficient design. The solutions proposed include in consequence a flexibilization of these hierarchies by recognizing the contextual relativization of the importance of the different sources of evidence or an improved design by complementing the existing sources with the neglected ones. I will further touch on these points in some detail.

The focal targets of the critiques are probably the issues related to RCT (randomized controlled trials). As mentioned they are placed at the top of

⁹ Montori & Guyatt in their 2008 paper "Progress in evidence-based medicine".

the hierarchy of evidence considered to be the ‘golden standard’ of evidence for effectiveness of medical interventions. One author even states “If the study wasn’t randomized, we’d suggest that you stop reading it and go on to the next article in your search.”¹⁰ But what is RCT and why is it so much valued?

Initially the technique was developed by the statistician Ronald Fischer and applied in agricultural studies. In the late 40s the technique was for the first time applied to humans in the landmark streptomycin trial. This opened the door for further application that became in the last decades a widespread used technique. According to a well-known textbook¹¹ randomized controlled trials are comparative studies with an intervention group and a control group; the assignment of the subject to a group is determined by the formal procedure of randomization. The main qualities of such a study are thought to be following¹²: It eliminates bias in treatment assignment,” specifically selection bias and confounding; “it facilitates blinding (masking) of the identity of treatments from investigators, participants, and assessors.”; “it permits the use of probability theory to express the likelihood that any difference in outcome between treatment groups merely indicates chance.” These qualities raised RCT them to the status of the ‘gold standard’ of medical research. Nevertheless the status is not regarded as well justified esp. in the aftermath of the critiques that were articulated in recent years.

Some the major critical voices from outside the medical professionals came from the British philosophers of science – the most prominent based at London School of Economics. I will make reference to these positions since they concentrate in a most efficient way the accused points. I will make reference esp. to the critiques developed by John Worall, Nancy Cartwright and Jeremy Howick. Worall criticizes the highly praised benefits of the randomization process. In his view randomization is just one way and not a perfect one, of controlling for confounding factors that might produce bias. For John Worall randomization

does not eliminate confounders entirely as usually claimed.¹³ It can control for most but not for all confounding factors esp. the unknown. Therefore we cannot be sure of eliminating bias induced just by accident and making the two compared groups different. A solution would be to re-randomize each time and to aggregate and analyze the results overall; but this is practically impossible.

Another line of critique fired by Worall is to accuse RCT as being too heavily grounded in the frequentist paradigm of statistical thinking. This was proposed by the statistician Fisher in this probabilistic frame and it builds on frequentist assumptions. The alternative is the recently influential Bayesian view which does not support this logic. As Sir Michael Rawlins also remarks in his Herveian Oratio: “Bayesian approaches to the design and analysis of RCTs are likely to play a much greater part in the future”. Indeed a growing number of statisticians believe that the difficulties inherent in the frequentist approach in design analysis and interpretation of RCT could be overcome in a Bayesian approach.

Jeremy Howick directs his critique against another procedural aspect of RTC: blinding or masking. Blinding refers to the procedures that aim to “keeping trial participants, investigators (usually health-care providers), or assessors (those collecting outcome data) unaware of the assigned intervention, so that they will not be influenced by that knowledge.”¹⁴ Many researchers believe that one of the strengths of RCT is double-blinding in which all persons are involved: participants, investigators, and assessors in being unaware of the intervention assignments. Howick argues that the two potential confounders ruled out by double blinding (involving the patient’s as well as the physician’s beliefs) are often not actual confounders outside placebo controlled trials of treatments with mild effects that have subjective outcome measures. Masking also seems to be ineffective in placebo controlled trials due to the presence of side effects.

Another influential author is Nancy Cartwright. Her critiques were mainly focused on the validity of RCTs. According to her view, one may accept that RCTs have internal validity, but applicability

¹⁰ S.E. Straus et colab. In their book *Evidence based Medicine: How to Practice and Teach EBM*

¹¹ In Friedman & colab. *Fundamentals of Clinical Trials*. Springer 1998.

¹² Kenneth Schulz & David Grimes in “*Generation of allocation sequences in randomised trials: chance, not choice*”, *The Lancet* 2002.

¹³ He presents his position synthetically in such papers as “*Evidence in medicine and evidence-based medicine*” (2007) or “*Evidence: Philosophy of Science Meets Medicine*” (2010).

¹⁴ Schulz & Grimes in “*Blinding in randomized trials: hiding who got what*”, *The Lancet* 2002.

to real world is dependent on the similarity of the test population and context to the population and context targeted by the intervention. These concerns are not unjustified and the history of RCT discloses many challenges to RCT-procedure due to exclusion of certain groups from participation (*e.g.* women, the elderly, children) being used nevertheless for general health recommendations. This generalization issue would also point to the fact that the participants are not actually randomly sampled. Among the reasons one may find the fact that the target population often has a number of comorbidities or that its members are often elderly and likely to be long-time users of the treatment. So it is common to select a study population in a way that allows them to test the healthiest people. Besides research trials are often conducted in contexts that differ in significant ways from the contexts of general practice.

Not least there are failures in practice as documented in some statistics that show that RCTs and meta-analyses are much more fallible than believed. Ioannidis¹⁵ for example looked at results from 59 highly cited original research studies and noticed that only 44% were replicated, 16% were contradicted by subsequent studies and 16% found the effect to be smaller than in the original study; the rest were not repeated or challenged. Other statistics disclose the fact that studies funded by pharmaceutical have an unexpected higher chance of showing effectiveness of an intervention than studies not funded by such companies. Among the factors that influence such statistics one might identify publication bias, time to publication bias and pharmaceutical funding bias. Some of them could be corrected as Salmon remarks¹⁶ but other are beyond such correction (such as funding bias).¹⁷

The more general conclusion that derives from the above critiques is that RCT are neither necessary nor sufficient for claiming unambiguously that we are getting knowledge from clinical trials. Its highest position in the hierarchy, the level of RCTs, meta-analysis and systematic reviews is not actually backed by a rigorous epistemic justification. In this light the most radical question

might ask how we should handle the main specific element of the paradigm – the hierarchies. Should we keep changing or improving them or should we distrust their guidance and drop them entirely. One may direct his critique on any such hierarchy as Stegenga does¹⁸ backing the view that none should be used in medical science even the latest and most-sophisticated one. The opposed view might nevertheless claim that there are still advantages in using hierarchies esp. the improved ones in offering at least some sort of guidance. Nevertheless one may argue that there might be other ways of organizing the different items such as a network of evidence¹⁹ paying closer attention to the interdependencies of different sorts of evidence.

Much of this reconsideration comes also from the critique that emphasizes the need to add and value other forms of evidence. Such are the ones from causal mechanisms or the theory-based explanations. Some authors even accused EBM of being rather statistical than scientific due to the devaluation of these forms of evidence. Clarke & collaborators²⁰ argued recently in a distinct way that evidence from causal mechanism should be considered alongside evidence from correlation (provided by RCTs). Since correlation is a poor indicator of causality, evidence of mechanisms might be more important in some cases. The last one is also required to get the first one (in order to set and evaluate RCTs) but also to generalize and apply causal claims.

The point for an increased valorization of the theory based explanations is made by such authors as Thompson or La Caze.²¹ La Caze argues for the role of basic science not only in specifying experiments, but also in analyzing and interpreting the data that is provided and is often also required in order to apply clinical research to therapeutic questions. Meanwhile Thompson²² points to the fact that EBM uses mathematics rather as a tool of analysis than as a language of science devaluing this way theoretical models. A future development

¹⁸ Stegenga in his recent paper “Down with the Hierarchies.”

¹⁹ As Bluhm does in “From Hierarchy to Network: a richer view of evidence for evidence-based medicine” (2005).

²⁰ In their 2013 paper “The evidence that evidence-based medicine omits”.

²¹ As for example in La Caze’s paper “The role of basic science in evidence-based medicine” (2011).

²² In the same paper mentioned at the beginning “Causality, mathematical models and statistical association: dismantling evidence-based medicine”.

¹⁵ In his 2005 paper “Contradicted and initially stronger effects in highly cited clinical research”.

¹⁶ Salmon in her 2011 paper “Just a paradigm: evidence-based medicine in epistemological context”.

¹⁷ Recent discussion on this issue could be found in Every-Palmer & Howick paper “How evidence-based medicine is failing due to biased trials and selective publication.”

is seen in this direction by authors like Sharma & Minhas²³, who make the case for EBM to “include models of disease underscored by evidence in order to integrate evidence, as it is currently defined, with the patient’s unique biology.” They try to illustrate from a patho-physiological perspective the benefits of such a move.

Now taking into account the many critiques and the way to respond one may stick with a general cautious optimistic position. This will probably embrace a methodological pluralism as the most pertinent position and could be implemented in various ways from flexible hierarchies to a typology of evidence.

FINAL MORALS

After twenty years of EBM dominance in medical thinking one might look at the possible morals that could we drawn?²⁴ The overall moral emerging from our discussion will clearly point to at the need to temper our initial enthusiasm and to recalibrate our expectation accordingly, in the light of the limitations expose by the numerous critiques. But how far should we go by rejecting or dropping the conception initial ideas – if we need to reject entirely some of them as the idea of hierarchies so central to this conception or only to amend and complement it – is still an open question. EBM is still very influential in medical thinking though some authors see it past its pick point as Salmon does²⁵. New paradigm might be on the rise such as the translational medicine, which could replace the EBM paradigm Nevertheless the EBM view does not seem to have exhausted its resources as much of today medical thinking is heavily influenced by it and much effort still flows into refining and accommodating the view to the new encountered issues.

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