RESEARCH

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Evidence-Based Medicine – A Paradigm Ready To Be Challenged?

How Scientific Evidence Shapes Our Understanding And Use Of Medicine

OPEN

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1 Introduction

> "Despite one popular caricature of 'the philosopher' as being somehow 'deep', the ones I know (coming mostly from what is known as the 'analytical' school) make it a point of honour never to have anything profound or clever to say on any matter whatsoever. In fact, they consider it the hallmark of a good philosopher that one is always prepared to ask the sort of naive question that others are too scared to ask, for fear of appearing ignorant."[1] (Michael Loughlin)

1.1 EBM — a unifying force in medicine?

Evidence-based medicine (EBM) was and is all the rage in medicine and the 'new way' to practice and teach medicine in our century. The term 'evidence-based medicine was coined in 1992 by scientists at the McMaster University, Hamilton, Ontario.[2] Today it is *the* established method in medicine, at least in what is called ‚allopathic' or ‚conventional' medicine and the term is by now part of the very fabric of medicine and of medical knowledge. EBM encompasses research, practice and the teaching of medicine, and many articles in peer review journals, and even entire journals, have dealt with the how and why and where of EBM since its appearance on the medical scene. However, it is still not quite clear what exactly EBM is, what exactly it encompasses and why it should be so much superior than other movements in medicine. The definition of EBM offered in the original paper by the 'Evidence-based medicine working group' 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 with the best available external clinical evidence from systematic research."[3] Sackett and colleagues have since refined the definition: "evidence-based medicine is a systematic approach to clinical problem solving which allows the integration of the best available research evidence with clinical

1 Michael Loughlin. (2009). "The basis of medical knowledge: judgement, objectivity and the history of ideas." in Journal of Evaluation in Clinical Practice. 15(6): 935.

2 Gordon Guyatt, et.al. for the Evidence-Based Medicine Working Group. (1992). "Evidence Based Medicine: A New Approach to Teaching the Practice of Medicine." in the Journal of the American Medical Association (JAMA), 268 (17): 2420 - 2425.

3 David Sackett, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. (1996). "Evidence based medicine: what it is and what it isn't." in the British Medical Journal (BMJ), 312: 71-2.

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expertise and patient values."[4] However, and although both of these definitions are still frequently cited, EBM has changed over time. Probably inevitably so because of its own growth factor, but also because EBM and associated terms can be, and are used, to further the cause of pharmaceutical companies and interest groups alike without giving EBM more credence or credibility.[5]

For many reasons EBM has still 'won' the claim to be the 'best' form of medicine of today against some competition. However, when evaluating EBM historically, it is not quite clear against what type or form of competition EBM had to actually compete. It seems more reasonable to argue that *some* sort of change in medicine was simply inevitable. The technical and inventional progress in medicine over the decades preceding the advent of EBM, including the first randomised controlled trials (RCTs), clinical trials which compare treatments with each other in two groups of patients and which were already performed before the method became part of a medical standard, was so profound that a rethinking of medical research and medical practice was the only possible consequence. Therefore it can be argued that EBM appeared on the scene at the right time and with the right instruments to pick up the different pieces of medicine and to attempt to unite them into one coherent system.

EBM was and is embraced by many physicians, clinicians and medical researchers, especially after it transpired that EBM can eliminate faulty medical reasoning that was prevalent over a long time. There are multiple examples available for this phenomenon. Many treatments that were widely accepted in the medical community up until the 1990's were discontinued after EBM had put them to the test and considered them to do more harm than good.[6] Prominent examples for this are the hormone replacement therapy (HRT) for menopausal women and the thalidomide scandal, causing birth defects, both of which will be discussed thoroughly in the coming chapters.

It is however important to clarify right from the beginning that there are treatments which will never be tested with the EBM methodology, since it would make no medical sense to do so. Treatments in this category are, for example, the removal of the appendix in the case of acute appendicitis, the Heimlich manoeuvre to unblock a blocked airway in a chocking patient or heart fibrillation to restart a

4 David Sackett, Strauss SE, Richardson WS,et al. (2000). *Evidence-based medicine: how to practice and teach EBM.* London: Churchill-Livingstone.

5 Trisha Greenhalgh, Jeremy Howick and Neal Maskrey for the Evidence Based Medicine Renaissance Group. (2014). "Evidence based medicine: a movement in crisis." in BMJ: 1-7.

6 Imogen Evans, Hazel Thornton, Ian Chalmers, and Paul Glasziou. (2011). *Testing Treatments: Better Research for Better Healthcare.* 2nd. Edition. London: Pinter and Martin: 3.

stopped heart.[7] These treatments, and many more, are proven to be the only effective treatment for the underlying disease. Cause and effect are directly observable and well established. Often however, pure observation is not enough to successfully establish a causal connection. Researchers and clinicians have, over the course of medical history, dealt with spurious correlations which looked plausible in the beginning, but where not so in the end. A wonderful example from the Middle Ages about such a spurious correlation that actually worked to a certain degree and therefore was widely accepted, are the masks of the plague doctors. Plague doctors wore a mask over their entire face with a long beak, a black coat with a cowl and a hat and gloves. The masks contained herbs because the assumption was that the plague was passed on by bad odours and therefore transmitted through the air. Patients suffering from the disease often stank badly because of their open and infected wounds.[8] In actuality, the plague is passed on through droplet infection. Since the infection was still airborne but based on bodily fluids, the masks and overall get-up helped, because they prevented the plague doctors of inhaling the infected droplets. The reasoning was spurious, the preventive 'treatment' nonetheless useful. If that is the case, it would be arguable that as long as the ends are achieved, the means do not matter. Unfortunately there are a lot of examples in medicine where spurious correlations led to very harmful treatments. One example out of the more recent medical history is about hormone replacement therapy (HRT) for menopausal women. HRT was considered to take away the unpleasant side effects of menopause and to even prevent certain types of cancer. And it seemed to work well. However, after conducting randomised-controlled-trials (RCTs), trials that compared HRT to either other treatments or no treatment, it transpired that HRT did not prevent these types of cancer, nor did it prevent possible heart attacks. On the contrary, HRT has considerable side-effects, ranging from headaches to cancer that were for some time swept under the carpet.[9] The reason why it was so "successful" was that it was most often prescribed in more affluent areas where many women were already in better shape, lived a healthy lifestyle and where overall more aware of their health and therefore better equipped to quickly deal with upcoming medical problems.[10] EBM and its rigorous methods prevented more women from receiving HRT and therefore prevented the treatment from doing more harm.

As well as EBM seems to function for all these examples, there are still many aspects of it that are not entirely explained, defined or understood, even by staunch

7 Jeremy Howick.(2011). *The Philosophy of Evidence-Based Medicine.* Oxford: Wiley Blackwell, British Medical Journal (BMJ) Books. Introduction: xiii.

8 Jacob L. Kool and Robert A. Weinstein. (2005). "Risk of Person-to-Person Transmission of Pneumonic Plague." in Clinical Infectious Diseases, 40(8):1166–1172.

9 Imogen Evans, Hazel Thornton, Ian Chalmers, and Paul Glasziou. (2011): 16.

10 Ben Goldacre. (2008). *Bad Science*. London: Fourth Estate: 108.

supporters of EBM. As with all ‚new' systems in an established field, EBM was and is not without its critics and their often very valuable criticisms and contributions.[11] EBM in general is enthusiastic about criticism, because medicine, like all sciences, advances through criticism and through asking the right questions. As will become obvious throughout the dissertation, some of these criticisms are aimed at improving EBM but some are just phrased to discredit the program altogether. This dissertation will defend EBM, albeit all its shortcomings, as the currently best way to conduct medicine. And it will offer a way forward to produce, understand, and use evidence in medical research, and, even more importantly, in medical practice.

1.2 EBM — one term used for different areas of medicine

EBM is by now sort of an umbrella term for multiple areas in medicine. Related terms are also in use, and most often their aim is to either be more specific or to 'solve' an apparent problem of EBM. Examples of such terms are: EBP for evidence-based practice[12] (I don't like using EBP because it also stands for evidence-based policy and even though both are context specific, there is a real danger of confusing them.) EBP can also refer to social work or education and therefore always has to be specified. EBHC which stands for evidence-based health care, EBN for evidence-based nursing and the number of abbreviations containing 'evidence' seem to increase daily. And the abbreviations seem to go in and out of fashion and therefore continue to be confusing. HTA stands for 'health technology assessment', and CER stands for 'comparative effectiveness research', these are two more terms that are interchangeably used with EBM but which do mean slightly different things and are themselves in need of clarification.[13] A fairly new term that appears by now in conjunction with, or as a contrast to EBM, is PCHC standing for 'person centred health care'.[14] PCHC is used in arguments both as an add-on to EBM and as a new way of looking at medicine. Therefore it is yet again not a term that can be used as such but is context-dependent as to its actual use.

11 Robert Smith. (2014). "Medical research—still a scandal." in the bmjopinion. http://blogs.bmj.com/bmj/2014/01/31/richard-smith-medical-research-still-a-scandal/. Last accessed on January 23rd, 2020.

12 K. Ann McKibbon. (1998). "Evidence-based practice" in Bulletin of the Medical Library Association 86(3):396-401.

13 Bryan R. Luce, et.al. (2010). "EBM, HTA and CER: Clearing the Confusion" in The Milbank Quaterly. Vol. 88.

14 European Society for Person Centred Health Care. www.pchealthcare.org.uk. Last accessed on January 23rd, 2020

Another example of a presumed 'alternative' is narrative-based medicine.[15] It claims that the patient's narrative, his or her story, is needed to make an informed decision about a medical treatment. However, in every patient assessment the personal history of the patient is taken and used as part of the treatment process. But narratives can never replace evidence. They are necessarily subjective and have to be understood by the physician in the wider context of the patients diagnosis. One improvement that a focus on narratives can bring to the diagnostic side of EBM might be that more time is spend on the wishes and values of the patient, already making the patient feel more comfortable in the medical setting.

All these terms and their underlying approaches and assumptions however are still somewhat part of EBM, because none of them would work without recourse to a solid medical evidence base. In every proposed scenario, from 'person-centred health care' to 'narrative based medicine,' the clinician nonetheless needs a solid foundation of medical evidence to make a treatment decision, and EBM seems to still be the only solution providing this solid foundation. The clinician can still decide to not use the 'best' available evidential treatment either because it does not fit the individual patients needs or it is not available at the point in time. However, this decision is only possible when the treatment options, based on medical evidence, are known. Even if the option is to forgo treatment, the associated benefits and risks are based on solid evidential grounds and can therefore be assessed and calculated, at least to a certain degree. There will always be an element of surprise in medicine, like spontaneous healing or remission, but even this element of surprise will to a certain degree be part of the calculation and decision on treatment, which by its very nature is based on mathematical possibilities.

For clarity's sake and because many of these terms are referring to EBM, are using evidence as their underlying base or are simply too confusing to use, the term EBM will be used throughout the dissertation. I will do so, however, with the important caveat that the term 'EBM' itself is in need of clarification. The most important distinction that should be made explicit when using the term 'EBM' is between evidence-based medical *research* and evidence-based medical *practice*, since these two areas differ widely from each other today and hence should be discussed separately, especially where ethical and methodological questions are concerned. The division of the term 'EBM' into 'evidence-based medical research' and 'evidence-based medical practice' will also be one of the key arguments of the dissertation, since it is that division which will make medical practice more person-centred. And making EBM more person-centred again will save it from much of the criticism levelled against it.

15 Trisha Greenhalgh. (1999). "Narrative based medicine: Narrative based medicine in an evidence based world." in BMJ (318).

1.3 The necessary division of EBM into 'evidence-based research' and 'evidence-based practice'

Medical research starts at the molecular level and aims to make inferences from there to the population level and tries to answer questions regarding all patients with a certain disease, illness or handicap. Medical practice, in contrast, deals with the individual patient and has to ask which treatment is the right one for this special patient, with the patient's individual circumstances, preferences and values taken into consideration.[16] The two areas of medicine, research and practice, are closely related and dependent on each other. But they are not the same and should be discussed in a separate manner and with a slightly different focus with regard to their ethical and methodological advantages and problems.

Although it would be tempting to use the abbreviations EBP, for 'evidence-based practice', and EBR, for 'evidence-based research', again it seems counter-intuitive to the usual use of the term 'medicine'. 'Medicine' has always encompassed both, practice and research and for the longest time it seems as if the two were so fluidly going hand in hand that a clear distinction between them appeared to be none-sensical. However, today with EBM in full effect and with the incorporation of all the medical advances of the last decades, research and practice are, sort of by necessity, two separate entities in medicine, often with different personnel involved, or even employing entirely different companies to perform research. Pharmaceutical companies are conducting their own research into new drugs and have changed how the science of medicine works considerably by focusing entirely on research and the production of drugs. Physicians are still the ones dispensing the drugs and researchers in a clinical setting are coming up with new drugs and treatments, but nevertheless pharmaceutical companies are a driving force in the production and marketing of drugs.[17]

Since medical trials, the evidential basis for EBM, and the hallmark of evidence-based research, are fairly complex to perform and need a special set up, it can be a methodological advantage to remove them from the regular running of a clinic or hospital.[18] Big university hospitals often can and do both, research and regular care, but they tend to be the exemption to the rule. And even if research and clinical care are happening in the same building, they are distinct from each

16 Julian Reiss and Ankeny, Rachel A., (2016). "Philosophy of Medicine" in The Stanford Encyclopedia of Philosophy (Summer 2016 Edition), Edward N. Zalta (ed.), https://plato.stanford.edu/archives/sum2016/entries/medicine. Last accessed on January 23rd, 2020.

17 Peter Konrad. (2005). "The Shifting Engines of Medicalization." in Journal of Health and Social Behavior. 46(1): 3-14.

18 Ben Goldacre. (2012). *Bad Pharma: How medicine is broken and how we can fix it.* London: Fourth Estate: 225. Ben Goldacre lobbies for large randomised trials which can happen in everyday medical care by integrating existing patient data. That would be a solution where care and research are combined.

to explain upcoming anomalies. The old and the new paradigm are, according to Kuhn, "incommensurable" because, or so he claims, scientists working in different paradigms do not even speak the same scientific language anymore and therefore cannot communicate meaningfully with each other. A valid criticism to this definition of a paradigm in science is that if the language would really be that 'incommensurable' then Kuhn, and everyone else who tries, should not even be able to explain different paradigms in a coherent and comparative manner.[21]

Kuhn claims that "Since new paradigms are born from old ones, they ordinarily incorporate much of the vocabulary and apparatus, both conceptual and manipulative, that the traditional paradigm had previously employed. But they seldom employ these borrowed elements in quite the traditional way."[22] That means for Kuhn that they do not share a common measure.[23] The terms the scientists are using do not have to same meaning from one paradigm to the next. Kuhn centres his incommensurability theory on specific examples like the shift from the Newtonian to the Einsteinian understanding of space and time. Admittedly, the shift here was a major scientific one and left some physicists, who were still believing in the Newtonian world view, stranded. The progress in medicine however does not seem to be comparable in magnitude to the Newton-Einstein example, or the shift from the Aristotelian to the Copernican understanding of the solar system.[24] Progress in medicine happened and still happens gradually and often slowly and not in seismic shifts which would make the old non-comparable to the new.

Trisha Greenhalgh, one of the proponents of EBM, claims, based on Kuhn, that the paradigm shift can also be triggered by a young generation of scientists who are not accustomed to the established paradigm and are starting to question its premises. Since these questions are not appreciated by the senior scientists, the young group branches out and establishes a new paradigm.[25] However, even if a younger generation is branching out and establishing a new view on the medical

21 Scott R Sehon and Donald E Stanley. (2003). "A philosophical analysis of the evidence-based medicine debate" in BioMedCentral Health Services Research 3(14).

22 Thomas Kuhn. (1996): 149.

23 Alexander Bird. (2013). "Thomas Kuhn", The Stanford Encyclopedia of Philosophy. Ed. Edward N. Zalta, https://plato.stanford.edu/archives/fall2013/entries/thomas-kuhn/. Last accessed on January 23rd, 2020.

24 Kuhn uses the example of Einsteinian and Newtonian physics and although for the most part that shift in the sciences really did happen, the Newtonian system is still used for example to explain gravity. In the realm of the microcosmos, Newtonian physics still holds. (Brian Greene. (2003). *The Elegant Universe: Superstrings, Hidden Dimensions, and the Quest for the Ultimate Theory.* New York: Vintage Books.)

25 Trisha Greenhalgh. (2012). "Why do we always end up here? Evidence-based medicine's conceptual cul-de-sacs and some off-road alternative routes." in Journal of Primary Health Care; 4:92-7.

problems, that is not a paradigm shift in the Kuhnian sense, since the overall medical language is still the same. The groups can communicate in a meaningful way, even if new terms are incorporated, like EBM itself, which has emerged as a new term. There is a lot of criticism levelled at Kuhn for his theory of scientific change. The problem with Kuhn's theory, especially for medicine is the 'incommensurability theory'. EBM in the early 90's brought something new to the medical world, a new approach to look at all the available evidence, to produce new evidence and to assess the available evidence. However, that 'something new' was not a radical change or an anomaly in an established practice that needed to be included in a new and different way. The 'new' approach was to acknowledge that not all of medical practice is and was actually based on the most robust evidence and that treatments are and were commonly used which could be outdated and might even be dangerous. The proponents of EBM also realised that medicine was not unified. Prescription and treatment habits did not only differ between countries, but very often between surgeries in the same country and sometimes even within a single surgery, if multiple clinicians were employed and were part of the decision making process.[26] The prescription and treatment habits were often based on previously learned approaches which were not questioned over time. One goal of EBM was to make these differences disappear and, in consequence, to provide all patients with the same, and if possible excellent, level of care.

Therefore it is arguable if EBM is and was far less a paradigm in the Kuhnian sense, but was far more an inevitable measure at the time, and to a degree even today, to incorporate the rapid medical scientific progress between the 1950's and the 1990's into everyday medical practice and teaching of medicine. Medicine was shifting because of the progress and the accompanying changes, and a unifying movement, like EBM, made it possible to shift it in such a way that medical research as well as patient-centred care became equal parts of the fabric of medicine by asking the right methodological questions but without devaluing everything that medicine had achieved so far.

EBM still works by using the available information technology of our time, i.e. the internet and all the medical search engines, online journals and medical publishing corporations that are coming with it. The authors of the original paper had already predicted that the amount of available information would be growing exponentially in the future and hoped that there would be a workable solution for the problem. Today one of the biggest challenges of EBM and all other approaches

26 Gordon H. Guyatt. et.al. for the Evidence-Based Working Group. (2000). "Users' Guide to the Medical Literature: XXV. Evidence-Based Medicine: Principles for Applying the Users' Guides to Patient Care." in JAMA 284(10): 1290-1296.


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2.6.3 External validity and n-of-1 trials

To quote Jeremy Howick again "one type of randomised trial, namely n-of-1trials have arguably the highest degree of external validity of any comparative clinical study."[144] N-of-1 trials consist of one patient who receives either the treatment under test or a placebo or standard. In most cases the participant receives the placebo and the treatment on alternate weeks or month. Hence, the trial population and the target population is equal to each other.

N-of-1 trials do sound like the perfect alternative to standard RCTs because of the guarantee of external validity, if internal validity is given. However, n-of-1 trials are less reliable than could be assumed on a first glance. Since they only involve one patient it can be impossible to ascertain if that patient has improved because of the treatment, or because of "spontaneous remission" or because of the placebo-effect.[145] And it is impossible to infer how close this one patient resembles other patients with the same disease. N-of-1 trials are really only applicable for patients with chronic but otherwise stable diseases. Psoriasis and atopic eczema are examples for those, since a patient can test different skin treatments and see over time which one works the best. However, for most diseases, especially those which are unstable and are quickly changing, n-of-1 trials are not feasible, because their results can not be extrapolated at all.

> "For example, it is impossible to know whether aspirin will prevent a patient's stroke until it is too late. This is a problem with most cases of preventive medicine, and also with treatments for many acute conditions, such as meningitis, pneumonia or snake bite, where we don't have the opportunity to test it in each individual patient and see. So we then have to rely on whether and how to apply the evidence from the experience of studying others."[146]

N-of-1 trials are therefore no solution to the overall problem of external validity but only provide a solution in very exceptional cases.

2.6.4 How can external validity be achieved?

External validity is hard to achieve and is lacking as main goal in many trial designs. Nonetheless, external validity is what is needed to make the trial results applicable to the target population and preferably to the individual patient. One solution described above, but only in very special cases, can be N-of-1 trials, but they are seldom feasible. The most obvious solution must be proper recruitment

144 Jeremy Howick. (2011): 55.
145 Jeremy Howick. (2011): 55.
146 Jeremy Howick. (2011): 152.

for trials. Since most people suffer from more than one condition, co-morbidities should not be discounted in the recruitment process but understood as known confounders and taken into account in the trial design. Women and children need to be included, in the case of children apparently only after careful consideration, into trial designs so that all age and gender groups are represented, depending on the disease and drug or treatment in question. That trials can carry a certain risk for the participant is acknowledged, but should not exclude the recruitment of all possible participants. In the next chapter I will discuss informed consent and the role it can possibly play in safeguarding participants as much as possible and how patients can be involved in the decision to participate.

Another way to make trial results more externally valid are phase IV trials. These happen after the market approval of a drug and can be either randomised trials or longitudinal observational studies. Goldacre proposes that, especially in cases where there are competing treatments for the same condition, large randomised phase IV trials should be conducted via a patient database to which every GP and clinician has access, at least in the UK. Germany has a fairly similar system. These databases are anonymising the data of the individual patient, but would provide the researcher with the overall number of patients having received a certain treatment and with the overall characteristics of these patients and observed adverse events or side-effects. Goldacre argues that when there is general uncertainty about which treatment is superior for a certain disease, the GP should use the regular prescription system, but instead of entering the patient data and printing a prescription, he would enter the patient into a randomised trial and either treatment A or B is assigned to the patient. The GP consequently reports in the follow-ups about the performance of the treatment and, over time, a patient population which benefits from either the one or the other treatment would be established.[147] The follow-up, at least in the UK, would be very easy and would not entail any more work for the GP, since all patient-data is recorded by a computer system anyway. Apparently the only methodological virtue missing in this scenario is blinding. But Goldacre argues that since existing treatments are compared, the methodological role of blinding is not as significant, since patients often do not have a preference towards either treatment. And the negative effect of non-blinding is calculated against the overall long-time effect of such a study, which can in theory run indefinitely. In the proposed circumstances the number of patients/participants is definitely big enough to make a statistical difference, and the treatments are not tested in an idealised trial population, but in the actual target population.[148] The problem of external validity is thereby solved. For a lot of diseases today there exists a standard treatment. New treatments are often either a variation of the standard or

147 Ben Goldacre. (2012): 227.
148 Ben Goldacre. (2012): 228.