

Perspective and future of evidence-based medicine

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ABSTRACT

Background: Evidence-based medicine (EBM) has evolved over a century. EBM is now the guiding principle of medical practice. High-level EBM usually derives from a well-designed, randomised, double blind, placebo controlled trial of parallel groups and sufficient number of patients enrolled. However, in recent times, concerns of EBM misguiding clinical practice have been on the rise. This paper aims at exploring the root cause of why EBM is perhaps losing its touch as the measuring standard of clinical practice.

Method: History of EBM and criteria of determining a well-designed and conducted trial were reviewed. The impact of pharmaceutical industry on EBM has been elucidated. The percentage of clinical trials that were sponsored by the pharmaceutical industry was calculated. Some of the wrong motives of conducting clinical research were identified.

Result: To some extent, EBM may have contributed to overdiagnose or overuse of medicine. Nearly 46% of clinical trials were financed by pharmaceutical companies. About 90% of manuscripts printed might not need to be published. Many trials contained at least one outcome that did not match its initial specification as registered.

Conclusions: While EBM continues to be the guiding principle, clinicians should be aware of potential tainted results. In the future, big data is likely going to offer us a new aspect of EBM and arm us with more comprehensive data when we make our clinical decisions.

Doctors put drugs of which they know little into bodies of which they know less for diseases of which they know nothing at all.

— Voltaire, 250 years ago



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Nearly 100 years ago, Sir William Osler, the Father of Modern Medicine and a medical educator, had pointed out the deficiencies of medical practice: poor understanding of history, disconnection between science and civilisation, and separation of technological progress from humanity. These three questions still exist today and are intertwined with the modern development and reformation of medicine.¹

HISTORY OF EVIDENCE-BASED MEDICINE (EBM)

EBM is a large system of theory that contains rich connotations. As defined, it is about the medicine that is based on the evidence. Using published literature, conclusion is often drawn based on the quality of the studies and data collected. These conclusions would offer guidance to physicians in clinical practice since we believe that these results have been derived with scientific rigour. EBM offers important clinical significance and scientific value. It emphasises on the natural course of the disease, intervention of illness not often by drugs, modern diagnostic standard, clinical research strictly regulating the conflict of interest, importance of long-term medical treatment and follow-up, and encouragement of the voice of opposition and those with questions. The purpose of creating EBM by our predecessors was mainly to fix the deficiency of clinical and experimental medical models in our daily practice. EBM has overthrown many suppositions, intuitions and hypothesis, and to a great extent changed our clinical practice. The best example is the publication of various clinical guidelines from the findings derived from randomised clinical trials. Here, the key is the quality of those randomised clinical trials. In order to evaluate the validity of the trials, the following criteria are often used: (1) reasonable design; (2) truly randomised; (3) bigger the sample the better; (4) sound statistics; (5) therapeutic parameters congruent to clinical practice; (6) ample follow-up time so that the results would reflect real practice; (7) clinically significant and applicable and (8) end point design, the more 'harder the data', the more clinically valuable.

THE ADVERSE EFFECT OF EBM WHEN IT IS MISUSED

EBM has helped us learn new knowledge from published clinical trials that have been well conducted. However, objective ways of

grading literature cannot help us subjectively differentiate false data. Recently, EBM has been questioned for its tendency of influencing physicians to practice incorrectly. EBM has become a 'loaded gun,' threatening the clinicians with potential penalty such as no-payment if they do not practice according to the so-called 'best evidence'. While one good use of EBM is to curtail medical waste, the fact is that medical overdiagnosis and overuse are getting worse and EBM may have played a facilitating role. During the 1990s, pharmaceutical industries began to be involved in EBM. Before then, physicians could resist the temptations of 'drug rep' because often the drugs from these drug companies lacked clinical evidence. Gradually, the pharmaceutical industry has realised that EBM was not a threat to them but rather an opportunity. If their drug research has been published in a reputable journal, this drug would likely be recommended by the clinical science and as a result, it would bring far more profit to the manufacturer than the effort of marketing by pharmaceutical representatives. This turn of the event has had far reaching effect on the use of EBM. This process is just like a famous quote on statistics: if you query the data, data would provide the answer. Most recently, an online survey conducted by *British Medical Journal (BMJ)* has revealed that 75% of physicians felt that EBM was collapsing. It has asked people to be aware of those commercials that relentlessly advertise the clinical trial results.

Without the backup of the so called 'evidence,' drugs would not have had a place in the guidelines. The fact is that many patients in our daily clinical practice do not fit those criteria used during clinical trials; consequently, prescribing these recommended medications could actually be harmful. Thus, directly financing and supporting of clinical trials by big pharmaceutical companies and having those results published, more or less would influence the writing of clinical guidelines. EBM itself now needs to reflect on this seemingly unavoidable influence. Although EBM itself is not a culprit, it can mislead. This negative impact could be far reaching. If this defect of 'cave of ants' size on a levee is not fixed in time, miles of levee might crumble soon.

It is the fact that overwhelming majority of research is relying on the financial support of pharmaceutical industry and such support is actually needed and not avoidable. Pharmaceutical industry therefore has had unobvious impact on the medical literature. Intentionally or not, pharmaceutical industry and EBM became intertwined and difficult to differentiate. Consequently, the indications for many drugs became broadened and clinicians felt that seemingly there was a drug for everyone condition.

Scholars have reviewed the Medline and Embase and studied several published randomised placebo controlled trials and performed a meta-analysis. They have discovered that more favourable results were found from pharmaceutical industry-supported trials than those financed by non-pharmaceutical industry (device)

groups. Even though many of these trials were double blinded and randomised, their results have been quite exaggerated.² Consequently, the screening and selection process of EBM under this circumstance has been twisted into a sort of 'healthy' branding, enhancing over-diagnoses, overuse and become the source of various law suits and symptoms.³

Then, why is it difficult to share big medical data in China? The main reason is the 'Mahjong' mentality and working only for us. Many practice by keeping 'an eye on your neighbour on the left and the other on the right'. Hence, sharing data with each other is very difficult.⁴ The essence of scientific research is to explore the unknown world and seek truth. However, many are motivated to do research for different reasons: promotion, raising social status, obtaining fame and money. Only a few truly study the literature. Many physicians obtain their new knowledge through participating in sponsored seminars. They may not realise that even the power point slide deck used for teaching are made by the pharmaceutical industry, not put together by the teaching physician. The lecturers are often the spokespersons for the pharmaceutical industry. On the other hand, the negative results of a trial would have no commercial benefit; hence, the negative findings are hardly mentioned. That is why publishing negative results of clinical trials is as important as the positive ones.

THE IMPACT OF MEDICAL JOURNALS ON EBM

David Sackett, the 'Father of EBM,' once said "Half of what you'll learn in medical school will be either dead wrong or out of date within five years of your graduation; the trouble is that nobody can tell you which half...". Research by the editors has shown that many medical literature are misleading and containing false-positive findings. No matter what kind of journal it is, close to 90% of papers need not to be published. Of 38 million already published papers, those that have been referenced for more than 200 times are <0.5%. Those that are considered classic writings and quoted >1000 times are rare. Nearly half have never been cited. Sceptics may say that the result of this analysis could only apply to the ordinary journals, not the leading ones. However, it was jaw-dropping when the elite journals were examined. The story of the 31 years old German scientist Jan Hendrik Schoen was infamous. He joined the Bell research laboratory and published 17 papers in *Nature* and *Science* within 4 years. He was considered a potential future Nobel Prize recipient. However, a scientific reporter was suspicious of his conduct and followed him for 4 years. The reporter finally provided the proof that all of his 17 papers were fabricated.⁵ People began to wonder why the leading journals publish papers based on fake data even though these journals have peer reviewers worldwide. Four reasons may possibly explain this phenomenon: small research project, marginal therapeutic effect, complex relationship between the

researcher and funding agency, and hotly competed research topics. One such example is a large-scale population screening trial for a condition that discount the individual difference, and once completed, its results are recommended to the general population at risk.

EBM AND THE ERA OF BIG DATA

The mission of a doctor is to heal the sick and save lives. The reality is that life itself is a sexually transmitted 'disease' that carries 100% mortality. On the other hand, it is true that many great medical discoveries came from close collaboration between the academia and manufacturers. However, it seems that the mission of the pharmaceutical manufacturer is financially driven and suspicious of intentionally labelling healthy people sick. In addition, it is difficult to find a specialist who has no tie with the biomedical or pharmaceutical industry. A recent American survey of 50 medical schools that own hospitals has revealed that every researcher has received on average \$33 417 capital assistance from an industry. US Food and Drug Administration also heavily relies on the funding from biomedical industry and in 2010, such funding has reached a total of \$1.25 billion, nearly 46% of its drug research budget.¹ To great extent, billions of sales profit has created trouble in clinical research. Scientific research has been 'stained by the stinkiness of money', filled with false information, wrong diagnosis and confused standards. Therefore, it has generated untrustworthy survey, statistically significant but clinically meaningless research results, misleading data, and hard to differentiate false data but somehow all have been easily published.^{6 7} One example is the recent announcement by a major pharmaceutical company that manufactures a drug for Alzheimer's disease. The company announced that it will continue on its clinical trials by eliminating patient's daily functional ability as an outcome measure. Although the reason behind this change was that patient with early Alzheimer's disease would have mild functional impairment and 18 months of trial could not detect it, one would suspect that such change could possibly affect the fate of this new drug, which has been closely watched by the medical profession.⁸

Another example that can illustrate this phenomenon was the Woman's Health Study, which enrolled 160 000 postmenopausal healthy women. The trial has found that women on hormonal replacement therapy had more breast cancer, heart disease, stroke and thrombosis than those in the control group. The price paid to treat these complications was far higher than the benefit of preventing colon cancer and hip fracture. This project was stopped 6 years into its originally planned 15 years of research. Another shocking example was the use of β -blocker in the Guidelines of European Heart Association. This recommendation was based on the fabricated research results from Holland researchers, which was possibly associated with nearly 800 000 deaths. These researchers initially found that perioperative use of β -blockers was

cardioprotective in two clinical trials. This finding was incorporated into the European 2009 guideline. Nevertheless, a recent meta-analysis of 11 clinical trials of the same topic has shown that patients treated with perioperative β -blockers had 27% more deaths than those in the control group, which was equivalent to 800 000 deaths in Europe.

It is undeniable that medical profession is influenced by potentially biased information from some publicised scientific publication. Although mandated by the top medical journals that all clinical trials should be registered online first, a recent *Journal of the American Medical Association (JAMA)* article has found inconsistency of information registered on clinicaltrials.gov and its final publication.⁹ The researchers selected 96 clinical trials published in 19 journals with high impact factor (>10). They have found that 70 trials were sponsored by the industries. The most popular areas of research interest included cardiovascular disease, diabetes and hyperlipidaemia (23%), cancer (21%) and infectious disease (20%). The results of these trials were published in the *New England Journal of Medicine (NEJM)* (24%), *Lancet* (19%) and *JAMA* (12%). Nearly 93–100% of these clinical trials published the information of cohort analysis, interventions and outcome. However, 93 of 96 trials contained at least one outcome that did not match the information registered. The inconsistency between the cohorts and intervention was about 2–23%. Ninety-one clinical trials generated 156 positive outcomes. Among them 132 (85%) described the findings in clinicaltrials.gov and journals, while only 14 were published in the website and only 10 in the journals.

We know well that the essence of EBM is to combine the best external evidence, physician's personal experience and patient's wishes together. All three are needed to help a physician make the most appropriate clinical decision when treating an individual patient. Randomised and controlled studies and meta-analysis are not equivalent to the EBM. They are the reflection of external evidence. When the external evidence is lacking, the experience of a treating physician becomes very important. In this era of big data, biomedical science will have a major role in the world and the use of internet can support transparency and honesty. The explosion of large data has made the traditional research methodology obsolete. Randomisation of samples could be replaced with a complete data set. Statistics has been in use for over 100 years and perhaps one day it will be outdated. The best statistical methodology is probably the exhaustive attack method, which is to have the entire data points at once: samples=entirety. In this era of big data, we could have digitised human body and data on an individual but not a cohort. Everyone can be defined at the individual level as a single entity. The force that has the impact on this change is the internet.

For the physicians today, the technology is ready but new concepts and ways of thinking are still lacking. The physicians of the future will not play the role of

knowledge storage but knowledge administrator. They should interact with the patients better, provide compassionate care, consult the patient, assist in decision-making process and be a partner with the intelligent patients. By focusing on solving clinical problems, they will apply the knowledge learnt from a complete set of data to their daily clinical practice and serve the patients even better.

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