Evidence Based Medicine: Making It Better

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Evidence Based Medicine began as a "bottom-up" paradigm that taught medical residents to search the literature for the best available evidence and to critically appraise it for making patient care decisions. As its popularity increased, there evolved a huge market for ready-made EBM summaries and reviews and there is now a scramble to provide this service. Those who provide the service come to wield tremendous influence and power. This article describes the evolution of this important tool and the pitfalls in how it is practised. People in the healthcare field need to understand all these aspects of EBM if they are to exploit its potential for public health.

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Evidence Based Medicine (EBM) is a buzzword today – it is used in the wider society outside of its originally narrow technical context, often pretentiously and inappropriately to impress and to make discourse appear esoteric, and technically sound. EBM has an enchanting image that reaches out to researchers and scholars (Holmes et al 2006). Also it has a ring of scientific authority that mesmerises decision-makers and government officials. Health planners value and purchasers and payers feel reassured by such authorisation. This article looks at the evolution of EBM and describes the pitfalls in how it is practised. People in the healthcare field need to understand all these aspects of EBM if they are to exploit its potential for public health.

The Beginning

EBM was originally developed as a method for teaching medical residents (Druss 2005). Keeping up to date with knowledge has become more difficult in the internet age. Coiera (2000) has shown how the exponential growth of information creates a poverty of attention. The low cost of production of poor quality information results in high quality information being drowned out, increasing the cost of finding specific information. It was estimated in 1992 that a dedicated doctor would have to study at least 17 papers every day to keep abreast (Davidoff et al 1995). Alongside this glut in information and data, the cost of medical care also increased with introduction of newer technology – many of them of doubtful utility. These developments resulted in enormous variation in the standard of care and costs of care. It is in this milieu that the term EBM was coined at McMaster Medical School in Canada in the 1980s to "make use of explicit search criteria to find the best available evidence" (Rosenberg and Donald 1995). EBM has been described by one of its leading lights, David Sackett, as the conscientious, explicit and judicious use of current best research evidence in making decisions about care of individual patients (Sackett et al 1996). It was expected that this would result in better care of patients. Costs would be curtailed by the avoidance of less useful technologies. Thus it began as a "bottom-up" paradigm that taught residents to ask answerable and focused questions, search the literature in a transparent and reproducible way to find the best evidence and to critically appraise it in an explicit and structured manner, often using mathematical analyses to give a clear idea of the strength, statistical significance and possible clinical significance of the results. This article also describes some of the risks attendant on its spectacular success in capturing the public imagination. It will touch on how vested interests have exploited its vulnerabilities.

The basic principles underlying the "evidence-based" practice movement are that there is a hierarchy of evidence and that modern informatics can make the evidence available to practitioners at the point of care. Clinicians should seek evidence from as high in the appropriate hierarchy of evidence as possible (Guyatt et al 2000). This was seen as a major shift away from traditional medicine that emphasised the expertise of the medical profession. The "freestyle" nature of "expert" critical appraisal was sought to be reined in (Malone et al 2002). It undercut the autonomy and authority of the doctor and the resultant variability in care breaking the stranglehold the profession had over how medicine is practised and compensated (Healy 2006). It was tremendously appealing to those who sought to impose uniform standards to assess performance and cost effectiveness. However EBM has had its critics. It was noted that the team that coined the term EBM considered using the phase "scientific medicine" but rejected it because it implied that other approaches were by definition unscientific (Guyatt 2002). They ignored the fact that the term "evidence based medicine" carries a similar moral valence and linguistic slipperiness (Sehon and Stanley 2003). Holmes and colleagues have castigated EBM because it excluded alternate forms of knowledge (Holmes et al 2006).

Newer definitions of EBM now acknowledge that research evidence alone is not adequate to guide action. It emphasises that clinicians must use their expertise to assess the patient's problem and incorporate the patient's preferences or values to research evidence before making management recommendations (Haynes et al 2002). It appears as if we have come a full circle, giving the clinician pre-eminence again, so much so that Druss (2005) has lamented the overly inclusive definition threatening to deprive the term of meaning. Sehon and Stanley (2003) have argued that the new definition merely says that EBM is the wise use of the best evidence available. They write that EBM defined in this manner cannot be thought of as revolutionary or even useful. After all who could possibly be opposed to using the best evidence wisely (Sehon and Stanley 2003)? They suggest that the debate between EBM and alternate approaches can change medical practice only if EBM ceases to be described in this "all embracing and vacuous" manner.

At the heart of EBM is the use of evidence hierarchies including randomised controlled trials (RCTs), systematic reviews and meta-analysis of RCTs. Alternative approaches to medical practice also take into account the patient's condition and values and hence this is not what separates EBM from the other approaches. What separates it is the priority it gives to certain forms of evidence (Sonnabend 2008). This essay will look primarily at the aspects that make EBM distinctive and revolutionary.

Systematic Reviews

Traditionally review articles were written for journals by "experts". Sonnabend (2008) writes that experts are often elevated to this rank by the marketing departments of drug manufacturers. It is not beyond conjecture, he says, that an expert has been created expressly to justify the claims of these manufacturers. In the review "experts" state their opinion about the proper evaluation and management of a condition, supporting key conclusions with selected references, and they have been shown to be both non-reproducible and as a scientific exercise of low mean scientific quality (Sackett and Rosenberg 1995). Oxman and Guyatt (1993) found that adherence to simple scientific principles in reviews were inversely proportional to self self-professed expertise of the experts.

EBM provided the framework for systematic reviews and the popularity of EBM has been helped by journals seeking explicit and transparent methods in reviews with bias-free list of citations. The hierarchy of evidence meant that the best evidence (that with the least chance of bias) was considered. Meta-analysis combines the results of several studies. In its simplest form, output of meta-analyses is the effect size where the weighting might be related to sample sizes of the individual studies. This aggregation of different studies helps overcome the problem of reduced statistical power in studies with small sample sizes.

Minor Flaws in EBM Concepts

For a meta-analysis to be meaningful all studies need to be included – both those that showed benefit and those that did not. It is usually hard to publish studies that show no significant results. Studies that fail to show benefit are not sent for publication and if they do, they are seldom published by editors. This "file drawer problem" where non-significant study results are hidden away from general view in someone's file drawer creates a serious base rate fallacy, biased or skewed distribution of effect-sizes and the overestimation of the significance of the published studies (Rosenthal 1979). An attempt is being made to overcome this file drawer problem by making registration of clinical trials mandatory. But the benefits of such a registry in meta-analyses have not been tested as yet. Also it has been suggested that the practice of using weights in a meta-analysis according to the sample size, rather than the size of the population they represent, may be misleading (Puliyel and Sreenivas 2005; Batham et al 2009).

This is best illustrated by the example of the blockbuster pain killer (anti-inflammatory drug) Rofecoxib (brand name Vioxx), which has now been withdrawn from the market. Initially, according to an editorial in the *New England Journal of Medicine*, peer-reviewed-literature was flooded by papers and RCTs from the employees of Merck and their consultants. There were epidemiological studies showing concerns about myocardial infarction and stroke with Vioxx but Merck claimed that only RCTs were suitable for determining whether there was any risk. There was an excess of 16 cases of myocardial infarction or stroke per 1,000 patients on the drug. Altogether 80 million people had received the drug before it was withdrawn (Topol 2004).

The appellation "evidence based recommendations" does not necessarily mean that the recommendations are based on firm empirical data. It only means that the

Box: Ranking Quality of Evidence

(Adapted from http://en.wikipedia.org/wiki/Evidence-based_medicine)

- Level A (Level 1): Randomised Controlled Clinical Trial
- Level B (Level 2): Case-control study:
- Level C (Level 3): Case-series study
- Level D (Level 4): Expert opinion or first principles

Categories of Recommendations

Level A: Benefits substantially outweigh risks

Level B: Fair evidence benefits outweighs risks

Level C: Balance between benefits and risks close

Level D: Risks outweigh benefits

Level X : Scientific evidence is lacking

The apparent mathematical precision is illusory.

There is sometimes little relation between ranking of evidence and the recommendation.

Evidence Based Recommendation for Management of Bronchiolitis

American Academy of Pediatrics Subcommittee on Diagnosis and management of bronchiolitis. Diagnosis and management of bronchiolitis. Pediatrics. 2006 Oct;118(4):1774-93

Recommendation Number	Intervention	Evidence Level	Category of Recommendation
2a	No routine use of bronchodilators	B	Recommendation
6a	Assess hydration	X	Strong recommendation
7a	Give O2 if SpO_2<90	D	Recommendation
11	Use of homeopathy	D	Option

1 The "file drawer problem" and bias of meta-analysis.
2 Harm from Hierarchy of Evidence.
3 "Best Available Evidence" confers EBM Status to Dodgy Science.

level of evidence is indicated alongside each recommendation. (See box for "quality of evidence" and "probability of harm over good" and how reviewers' "judgment" relates to the "recommendations" made. It shows how recommendations based on opinion, not substantiated by any study data can be provided as evidence-based consensus-statements/recommendations.)

Along with the popularity of EBM the complexity for evaluating evidence has increased. No longer is it an amateurs' enterprise. Multiple data bases are explored, the references in the papers are further handsearched for new references, clinical trials registers and conference proceedings are scrutinised and pharmaceutical companies and individual researchers are contacted for unpublished data and ongoing trials. It is now being felt that most practitioners are not able to keep up to date by learning evidence-based strategies but are willing to seek out EBM produced by others. Busy clinicians are provided a detailed report and through a process of dumbing down EBM, also a one line answer called "clinical bottom lines" (Puliyel et al 2004). Thus there evolved a huge market for EBM summaries and reviews and a scramble to provide this service. Those who provide it come to wield tremendous influence and power and have introduced methodological refinements making the process more and more complicated to minimise the competition from copycat start-ups.

Funding and Bias in Conclusions

Theoretically, well blinded RCTs provide incontrovertible evidence. However empirical evidence has shown repeatedly that randomised trials are more positive if funded by for-profit organisations (Davidson 1986; Kjaergard and Als-Nielsen 2002; Djulbegovic et al 2000; Bekelman et al 2003; Lexchin et al 2003). Als-Nielsen and colleagues have shown that association with for profit organisations had little impact on treatment effect but the conclusions were more positive due to biased interpretation of trial results (Als-Nielsen et al 2003). Lundh and colleagues have shown that publication of industry-supported trials was associated with an increase in journal impact factors and revenue (Lundh et al 2010). Smith (2010), the former editor of the *BMJ*, has suggested that publishing the RCT sponsored by one drug company could yield a million dollars in the sales of reprints alone. According to Marcovitch – another *BMJ* editor, potential conflicts arise when the journal or publisher receives a substantial proportion of its income from reprints (23%, Massachusetts Medical Society – publishers of the *New England Journal of Medicine*; 41%, *The Lancet*; 53%, American Medical Association publishers of the *Journal of American Medical Association* (Marcovitch 2010). There is therefore an obvious publication bias favouring drug trials sponsored by the pharmaceutical industry.

Funding of Systematic Reviews and Meta-analyses

Yank and colleagues found that not just RCTs are biased by industry funding – even meta-analysis done by persons with financial ties to drug companies are likely to come to more favourable conclusions although not with more favourable results (Yank et al 2007). It is therefore important that meta-analyses are done by not-for-profit organisations. The Cochrane Collaboration is a rapidly growing international group of researchers who form an unselfish collaboration to provide evidence from systematic searches (Sackett and Rosenberg 1995). However as the group becomes bigger it becomes easy for those with vested interests to infiltrate the organisation. The Cochrane review on surfactant illustrates the point clearly. Surfactant is a substance that is put into the airways of premature babies to help them breath easier. The drug is expensive and meta-analysis showed that its use did not improve survival. However the Cochrane review says the drug reduces "neonatal mortality" (Soll 2000). The author who has declared conflicts of interests (payments in the past from many surfactant manufacturers) did a further analysis and found there were more children surviving the first 30 days of life (neonatal age group) and although there were no differences in mortality prior to discharge from the hospital he was able to write in the abstract that it reduces neonatal mortality and in the conclusion that it reduces mortality. Although this anomaly has been publicised in the *BMJ* (Tiwari et al 2004), this misleading statement has not been revised in the updated meta-analysis (Soll and Ozek 2010).

Dangers of Agenda-driven Bias

Wikipedia suggests that the most severe weakness and abuse of meta-analysis often occurs when the person or persons

doing the meta-analysis have an economic, social or political agenda such as the passage or defeat of legislation. "If a meta-analysis is conducted by an individual or organisation with a bias or predetermined desired outcome, it should be treated as highly suspect or having a high likelihood of being junk science. From an integrity perspective, researchers with a bias should avoid meta-analysis and use a less abuse-prone (or independent) form of research" (Wikipedia 2011). However reviews often ignore this warning. In the Indian context the Cochrane Database of Systematic Reviews recently published a protocol that illustrates the point poignantly (Kapoor et al 2010). The protocol states that the rationale for the systematic review is a public interest petition in the Delhi High Court questioning the introduction of newer vaccines and vaccine combination (DPT vaccine combined with Hepatitis B and H Influenza B vaccines) in the public health system by the government, under the influence of vaccine manufacturers and international agencies like World Health Organisation (WHO), without proper epidemiological and clinical studies (Delhi High Court 2009). The Indian Council of Medical Research and the National Technical Advisory Group on Immunisation (India) are named as respondents. Yet the new review to be done by the South Asian Cochrane Network is to be performed by the very persons who were party to the impugned recommendation (Subcommittee 2009).

Conclusions

Holmes has written that EBM groups like the Cochrane Collaboration have a profound sense of entitlement – what they take as a universal right to control the scientific agenda. In a polarised world it is as if you either embrace them or else be condemned as recklessly non-scientific (Holmes et al 2006). The picture may appear hopeless. Marcia Angell (2009) editor of the *NEJM* for 20 years writes, "It is simply no longer possible to believe much of the clinical research that is published or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion which I reached slowly and reluctantly over my two decades as an editor of the *New England Journal of Medicine*".

All is not bleak, however. Shakespeare has pointed out: "Though all things foul would wear the brows of grace, yet grace must still look so" (*Macbeth*). Although a lot of junk science purports to be EBM, we must not discredit everything that carries the name. A healthy scepticism and more widespread appreciation of the misuses of the label will make EBM better. One hopes it will somehow reincarnate to live by its original bottom-up paradigm.

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