LETTERS TO THE EDITOR

To the Editor

Evidence Based Medicine – A Sorcerer's Apprentice?

Re: The Evidence-based Medicine Paradigm: Where are We 20 Years Later? Part 1.

Can J Neurol Sci. 2013;40: 465-74

The Evidence-based Medicine Paradigm: Where are We 20 Years Later? Part 2.

Can J Neurol Sci. 2013;40: 475-81.

Evidence based medicine (EBM) has established itself as the foundation on which clinical practice is based. There is growing concern, however, that current information is of uncertain quality and credibility[1] and the literature may be biased, misleading and potentially harmful[2,3]. In their excellent two-part review Seshia and Young[4,5] highlight the shortcomings of slavish devotion to this concept, some of which deserve elaboration.

Uncertainty plagues medical decision making and EBM attempts to salve the medical conscience by providing mathematical proof that any choice is well beyond reasonable doubt. This goal is achieved by determining the probability of being wrong by statistical analysis. Therein lies the first misconception for statistical significance and clinical relevance are not synonymous and according to one group of mathematicians may concur by sheer coincidence[6]. Results are often expressed in the enticing but completely misleading context of relative rather than absolute risk. For example consider the risk of a particular intervention to be 2% in the control group and 1% in the treatment group. The relative risk reduction is 50% but the absolute reduction only 1% which is clinically irrelevant. Such data are presented to justify the exponential rise in statin prescriptions where mortality and non-fatal myocardial infarction have relative risk reductions of 19% and 29% respectively but absolute reductions of only 1.9% and 3%[3].

The second misconception follows the first whereby in a further attempt to reduce the risk of statistical error data are pooled from randomised clinical trials (RCT) and re-analysed by meta-analysis. Although increasing the sample size under scrutiny reduces random error, systematic error due to selection, misclassification and confounding biases will not be eliminated. Furthermore, despite numerous pleas, the studies included for systematic reviews may not contain unpublished or negative data[1] and duplicate publications may skew the results.

The third erroneous assumption is that, by comparing statistically matched homogeneous groups of patients, RCTs are the ultimate tool to provide the correct answer. In essence there is no such entity as a perfect RCT, for even with an appropriate sample size, assignment and blinding, each group, by the very nature of Gaussian distribution, will be heterogeneous. Evidence based medicine ignores this fact of life. The results therefore merely indicate what risk or benefit will be conferred upon the average population but, as quoted by Seshia and Young,[4] individual patients are neither means nor medians. As observed by William Osler no two patients react alike to a disease process. In complex situations such as critical care where numerous confounders exist, where therapies are titrated against physiological end-points rather than fixed dose regimens, and patients' reactions to a disease are unpredictable, the RCT will not provide reliable evidence[7].

Statistical purists cite intention to treat (ITT) methodology as the gold standard for RCT analysis. Following patient randomisation data are analysed regardless of drop outs or crossovers. This has no clinical common sense and is epitomised by the Endovascular Aneurysm Repair (EVAR) trial for high risk patients with abdominal aortic aneurysms deemed too unfit for open surgery. Of the control group 34% underwent aneurysm repair for a variety of reasons. ITT analysis showed a significant reduction in aneurysm related deaths with EVAR but no improvement in overall survival at eight years. Per protocol (PP) analysis however, not only showed a much greater reduction in aneurysm related deaths but a marked improvement in overall survival. Both effects were even more evident using the as treated (AT) technique. In addition to an ITT analysis, authors should declare non-compliance and provide an analysis that excludes these patients.

Of greater clinical importance and divorced from statistical probability are the concepts of number needed to treat (NNT) and number needed to harm (NNH). Number needed to treat is the reciprocal of absolute risk reduction and describes the number of patients who need to be treated for one to gain benefit. Number needed to harm identifies how many patients may be injured by the intervention within the NNT group. In the Postoperative Ischaemic Evaluation (POISE) study of peri-operative beta blockade, for every three patients spared a non-fatal myocardial infarction one would suffer a cerebrovascular event of whom only 15% recovered full function. The risk and benefit is therefore a matter of clinical judgement and patient preference, not mathematical probability.

Statistical vagaries notwithstanding, there are other confounders regarding the validity of the current literature. The influence of the pharmaceutical industry, financial academic affiliations, fraud and data fabrication have all reared their ugly heads as a medical hydra. These have cast an uncomfortable shadow over the literature with suggestions from highly respected editors that the literature lacks scientific credibility[1].

All will agree that we need to know the optimal treatment for our patients. At best, EBM offers an average choice but does not necessarily indicate the ideal intervention for an individual. Unless the shortcomings outlined succinctly by Seshia and Young, are appreciated untold harm may befall our patients. As concluded by Heneghan and Godlee[1], the future of healthcare hinges on how we deal with these challenges.

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Response to the Letter to the Editor

Re: Evidence Based Medicine – A Sorcerer's Apprentice? Can J Neurol Sci. 2014;41:128

We thank Dr. Muckart for his contribution to the dialogue on the Evidence-based medicine (EBM) paradigm[1], a major objective of our review[2]. His comments on the role of randomized controlled trials in critical care reinforce our own on Neuro-intensive care[3].

In addition, while conducting a recent search for references, using the search term "Critical appraisal," one of us (SSS) came across an article by Professor Jenicek (Canada), *"Evidence-based medicine: Fifteen years later. Golem the good, the bad, and the ugly in need of a review?"*[4] It seems inconceivable that we could have overlooked so intriguing a title, despite using the search term "evidence-based medicine" in our reference search[2,3]; but we must have, since Jenicek includes "evidence-based medicine" as one of the key words;[4] the article appears when we (now) use the search phrase: "evidence-based medicine and Jenicek." Our inadvertent omission, for which we apologise, draws attention to the potential for human error in scientific academic endeavours; can Cochrane (systematic) reviews be exempt?

The authoritarian teachings of some EBM experts and our often unquestioned acceptance of evidence, justify the analogy with the *"Sorcerer's Apprentice"* (who cannot control his broom)[1] , and to *"Golem"* (an obedient servant who can become dangerous)[4]. Reasoning and critical thinking must always be the very core of EBM healthcare and practice[4]. Evidence-based medicine has served us well, but must undergo continuous critique and improvement[1-5]. Jenicek said it well: "Being critical of EBM does not mean its denial, but rather a will to see it improve"[4].

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