Evidence Based Medicine: Practicing with Science

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In spite of a population that is increasingly less healthy, the average visit to a family physician in the United States decreased from 19 minutes in 2003 to 12 minutes in 2012. The current American reimbursement model, in which physician compensation by insurance companies is only moderately affected by the complexity of care, drives physicians to categorize patient visits types as short, medium, or long based on the numbers of diagnoses evaluated and treated. The fewer the diagnoses and less time spent in a given visit type, the better the physician is compensated. Because insurance companies negotiate significant discounts for contracted physician practices, a physician may have to see over 20 patients in a given day before he breaks even. He can see four short visits (CPT code 99213) in the amount of time he would spend with one long visit (CPT code 99215) and in doing so, generate more money. In an attempt to encourage this kind of reimbursement, some physicians post notices in their exam rooms exhorting patients to “present only one problem per visit”. These time pressures result in abbreviated patient histories and rapid, superficial diagnoses that are treated with protocols generated through “evidenced-based medicine” produced by pharmaceutical companies, an approach that is full of bias and profit-driven.

What is evidenced-based medicine (EBM)? The Oxford Centre for Evidence-based Medicine uses the original 1996 definition of EBM as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.” The challenges of EBM are two-fold: 1) definition of what constitutes current best evidence; and 2) the application of this evidence to the individual patient.

The first challenge, determining what qualifies as best evidence, can be daunting for most physicians. The average family physician spends 53 hours per week at work, seeing patients and doing paperwork. This leaves little time for researching what constitutes the current best evidence for the multitude of conditions for which they provide care. In addition, most physician lack the statistical training necessary to adequately evaluate and understand studies, leaving them vulnerable to accept exaggerated or distort claims. As a result, most physicians rely on summaries of original research to identify best clinical practices, turning to the opinions expressed in association guidelines and summaries presented in meta-analyses, in addition to limiting reading to mainstream medical journals.

Unfortunately, association guidelines may not accurately represent best science. Take for instance, the case of the American College of Occupational and Environmental Medicine (ACOEM) and the American Academy of Asthma, Allergy and Immunology (AAAAI) guidelines, published in 2002 and 2006 respectively. These guidelines reported that mold and mycotoxins could not produce human illness. Seriously flawed in their interpretation of the prevailing scientific research and relying on faulty science for their consensus statements, the ACOEM paper based much of its guidelines on an opinion paper by Bruce Kelman and Ronald Gots, the defense consultants in a water damaged buildings (WDB) litigation case, with insufficient understanding of how WDB cause human illness.

The Gots/Kelman 2000 paper

reports no use of methods for its conclusions, …no accepted epidemiologic standards for its approach. Their **assumption** is that the main route of mycotoxin exposure in humans is ingestion….The statement regarding ingestion in the Gots/Kelman paper **has no cited references for humans**. (Shoemaker, 310-311; original bold)

Kelman and Gots themselves admit that “such one –time *inhalational studies* ‘do not represent exposure to mycotoxins at chronic, low exposure levels from molds in indoor settings.’ Yet this admission, one that completely destroys their house of cards is never discussed (Shoemaker, 311-312).”

The Gots/Kelman paper in turn relied on one study, which asked the question of whether mold exposure affected rats (yes). In this study, Rao, et al, did a one-time instillation of washed (with methanol) mold spores into the trachea of Sprague-Dawley rats. No measure of the amount of toxin to which the rats were exposed was recorded but the rats suffered significant inflammation. Gots and Kelman state that since (they argue) the mechanism of disease in humans is through ingestion rather than inhalation and that humans would not be able to ingest sufficient amounts of mycotoxins, and despite the fact that the rats demonstrated significant inflammatory response to the mold exposure, mycotoxins could not cause illness in humans.

Rao and the coauthors of the rat study cautioned that the results of their research could not be used to determine the effect of exposure in humans.

In addition, the **authors** of the rat study **themselves** say that extrapolation **cannot be made** from the results of the limited, one-time, high-dose exposure in animals to long-term, low-dose exposure in humans. Indeed, they say the results aren’t the same as in chronic low-dose exposure. (Shoemaker, 317; emphasis original)

Shoemaker explains in great detail how both the ACOEM and AAAAI 2002 and 2006 guidelines are flawed. Citing a paper by Craner and an article in the Wall Street Journal that expose the bias and concealed conflicts of interest of the three ACOEM authors, he writes, “There is nothing evidence-based in either ACOEM or AAAAI as that process begins with the observation of affected patients (307).” Clearly, Dr. Shoemaker understands the Oxford Centre for Evidence-based Medicine’s definition of EBM.

Meta-analyses are considered by some to be the top of the pyramid for strength of evidence because they “thoroughly examine a number of valid studies on a topic and mathematically combine the results using accepted statistical methodology to report the results as if it were one large study (Duke).”  But the Oxford Centre for Evidence-based Medicine qualifies the strength of systematic reviews by its degree of homogeneity, a review “that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies (CEBM2).” Since primary care physicians frequently rely on this kind of study for evaluation of treatment options, it is imperative that studies have a high degree of homogeneity. “If it is well conducted, the strength of a meta-analysis lies in its ability to combine the results from various small studies that may have been underpowered to detect a statistically significant difference in effect of an intervention (Russo).” Unfortunately, assuming homogeneity can lead to false reliance on the findings of a meta-analysis, which may be flawed in the degree to which combined studies are similar. In an article published in the Journal of Family Practice, Monaco, et al, recommended that physicians “stop recommending omega-3 fatty acid supplements for cardiovascular protection. They have no significant impact on all-cause mortality, acute myocardial infarction, sudden death, or stroke (Monaco, 2013).” This “A” strength recommendation was based on a meta-analysis by Rizos, et al. published in JAMA, which included 20 randomized controlled trials (RCTs) with a total of 68,680 patients, with a median age of 68 years. Of the 20 trials included in the analysis, 13 looked at omega-3 polyunsaturated fatty acids (PUFA) as secondary prevention, 4 studied effects in both primary and secondary prevention, and 3 evaluated outcomes in patients with implantable cardioverter defibrillators. The mean daily dose of omega-3 PUFA across the studies was 1.5 grams daily, but only 12 used a dose of more than 1 gram daily and two relied only on dietary sources of omega-3 PUFA. Half of the studies were performed before 1998, before the routine use of statins for heart disease prevention. While the meta-analysis found a trend towards a decrease in all-cause mortality (RR of 0.96) and cardiac associated mortality and morbidity in patients taking omega-3 PUFA, this trend was not considered significant. No harmful effects of omega-3 PUFA were found in any of the studies. A supplement deemed to be harmless is shown to have a non-significant but measurable benefit in cardiovascular risk by meta-analysis. But a closer look at the studies included in the meta-analysis reveals that fewer than half used more than 1 gram of omega-3 PUFA, and there was no analysis of the relative amounts of eicosopentaenoic and docosohexanoic acids included in these trials. The average duration of the trials was 2 years. In 2013, Casula, et al, writing in Atheroscler Suppl, found “evidence that long-term effect of high dose omega-3 fatty acid supplementation may be beneficial for the onset of cardiac death, sudden death and myocardial infarction among patients with a history of cardiovascular disease.”

Meta-analyses begin with broad literature reviews in order to find a number of articles that address the clinical question posed by the analysis. In 2010, Fournier, et al reported a “patient-level” meta-analysis of the use of antidepressant drug effects and depression severity. The JAMA article identified 2164 citations that met the analysis criteria, of these 1883 were excluded for not meeting the study criteria. Of the 281 citations retrieved, 258 were excluded for criteria such as not being placebo controlled, using placebo washout, reporting less than a 6 week duration, not including Hamilton Depression Rating Scale (HDRS) scores. 23 study authors were contacted but 17 were excluded because they could not provide patient-level data (13) or they did not respond (4). Thus out of 2164 potential studies, only six met the authors’ criteria for evaluation of patient-specific results. When the original study data were analyzed, the authors found that in patients with mild to moderate depression (HDRS below 19) there was no significant difference in treatment between placebo and drug. For patients with severe depression (HDRS 19-22), there is some benefit, but the authors found that drug/placebo difference were found to have a medium-sized effect for patient with HDRS scores of 25 or greater and a large effect for those with HDRS of 27 or greater.

Fournier’s article created an up-roar at the time it was published. The surprising results shed light on the significant impact of bias in the medical literature. Pharmaceutical companies such as Eli Lily, the manufacturer of Prozac, seek to find new ways to extend their patents in a way to generate more profit from a drug. When the patent for Prozac was expiring, Eli Lily fabricated a new diagnosis, Premenstrual dysthymic disorder (PMDD; yet to be assigned an ICD-9 code), for which selective serotonin reuptake inhibitors (SSRIs) are prescribed for only 1-2 weeks at a time, despite the reported 3-8 weeks required for SSRIs to take full effect. Studies funded by pharmaceutical companies, often ghost-written by pharmaceutical company employees, selectively report results that demonstrate benefit of their drug while omitting data that does not coincide with their preferred conclusions. There is a bias towards publication of studies reporting positive results (i.e., a significant finding) versus those that report a negative (supporting a null hypothesis) or inconclusive. As a result, investigators tend to under-submit papers with negative results and some study authors employ “data dredging”, the mining of data for results that are significant and favor the desired outcomes and pharmaceutical results. “The selective publication of health studies could restrict doctors from carrying out optimal evidence-based medicine, which relies on reviewing and evaluating clinical outcomes that are communicated in peer-reviewed journals (Sergo).”

Efforts to require that authors register a trial before it begins so that negative results are not omitted from publication have not resulted in routine registration and only half of the studies posted in ClinicalTrials.gov are published. In 2004, the editors of top medical journals such as the Journal of the American Medical Association, the Lancet, and the New England Journal of Medicine, announced that they would not publish research, but despite this requirement even these prominent journals continue to publish articles that do not meet their criteria. In 2008, 94% of studies of antidepressant trials published in the New England Journal of Medicine showed positive results when in reality, only 51% of studies registered with the FDA demonstrated positive results.

Setting aside the issue of bias, medical findings often do not stand the test of time, “80 percent of non-randomized studies (by far the most common type) turn out to be wrong, as do 25 percent of supposedly gold-standard randomized trials, and as much as 10 percent of the platinum-standard large randomized trials (Freedman, Atlantic).” And when Ioannidis looked at the top 34 of the 49 landmark research findings in the past 13 years (the most widely cited articles that appeared in the most widely cited journals) that had presented effective interventions which were subsequently retested, 41% “had been convincingly shown to be wrong or significantly exaggerated (ibid).”

Yet despite the aforementioned problems with the evidenced-based medicine as it is understood and practiced today, the concept remains the ultimate goal for the optimal practice of medicine. As the Oxford Centre for Evidence-based Medicine states in its definition, EBM is “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.” This definition has two inherent components: 1) identification of what constitutes best evidence; and 2) the application of this evidence in the care of individual patients. As we have seen, given the challenges in which medical studies are evaluated in practical terms does not necessarily identify the best evidence, but rather the evidence put forward by pharmaceutical companies, or influenced by a few individuals, who may have a conflict of interest due to ties to the pharmaceutical industry. Further, the forces of financial reimbursement and restricted time limits the application of this evidence in a conscientious, explicit, or judicious manner. The patient is forgotten, his/her case is put in the paradigm of a protocol that treats all patients equally, and the power of quality studies is adulterated.

Contrast this prevailing state of EBM in the rushed, time-limited practice that is medicine today, with the authentic use of evidence by which to base the practice of medicine, as developed by Dr. Richard Shoemaker. Dr. Shoemaker is a family practice trained physician who embraced the basic science and clinical medicine he learned in medical school and residency and refused to abandon this approach to patient care. When his patients began to exhibit a mysterious illness, he investigated their illness and determined that a pfisteria outbreak in the Pocomoke River had caused their symptoms. But he didn’t abandon his patients to the powers of governmental agencies like the CDC or the local health department. He continued to investigate and to look at the science and the best evidence in order to better understand what was going on in these unfortunate people. And when one patient’s symptoms began to improve while taking a medication for another diagnosis (cholestyramine for high cholesterol), he pursued the possible reasons why this might be. Dr. Shoemaker’s investigations caused him to explore microbiology, biochemistry, and to translate the basic science that he read into plausible explanations for his patients’ illness. The more he learned, the more he investigated, and he left no stone unturned. Now, years later, he has published eight books and numerous articles in scientific research journals on biotoxin illness, including studies documenting response to care that are quantifiable and reproducible. This then, is evidenced-based medicine in practice: individualized evidenced base care, with an emphasis on the individual.

Perhaps one of the most striking differences between the EBM model as it is generally understood in medicine, and the individualized evidence based care as it is practiced and taught by Dr. Shoemaker, is the presence or absence of financial drivers. Profit drives the majority of the studies that are published in peer-reviewed journals. Care drives the work of Dr. Shoemaker. Using basic science research, and thoughtfully applying hypotheses in the care of individual patients, with appropriate institutional review board (IRB) supervision, Dr. Shoemaker is a model for the medical community. The lessons learned from his practice are simple: Question, think, research, and think some more. Assume nothing and believe no one without verification. Practice medicine as if someone’s life depends on it. It does.

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