Journal of Clinical Epidemiology 84 (2017) 14–17

Why evidence-based medicine failed in patient care and medicine-based evidence will succeed

Ralph I. Horwitz[a,*], Burton H. Singer[b]

[a]Department of Medicine, Temple Transformative Medicine Institute, Temple University, 3500 N. Broad Street, Philadelphia, PA 19140, USA
[b]Emerging Pathogens Institute, University of Florida, P.O. Box 100009, Gainesville, FL 32610, USA

Abstract

Evidence-based medicine (EBM) has succeeded in strengthening the evidence base for population medicine. Where EBM has failed is in answering the practicing doctor's question of what a likely outcome would be when a given treatment is administered to a particular patient with her own distinctive biological and biographical (life experience) profile. We propose Medicine-based evidence (MBE), based on the profiles of individual patients, as the evidence base for individualized or personalized medicine. MBE will build an archive of patient profiles using data from all study types and data sources, and will include both clinical and socio-behavioral information. The clinician seeking guidance for the management of an individual patient will start with the patient's longitudinal profile and find approximate matches in the archive that describes how similar patients responded to a contemplated treatment and alternative treatments.

Keywords: Evidence-based medicine; Personalized medicine; Medicine-based evidence

Evidence-based medicine (EBM) has succeeded at the narrowly defined task for which it was best designed, to evaluate treatment efficacy by estimating the average results in randomized controlled trials (RCTs). Where EBM failed is in providing evidence to guide decisions in clinical care for individual patients. In the sections that follow, we describe the success of EBM, indicate where and why it failed, and suggest what is needed in the new era of personalized medical care.

1. The success of EBM

The RCT and meta-analyses of multiple trials of the same topic (disease and treatment) are the major tools of EBM. It is worth remembering how recently the RCT was introduced into medical research. Although R.A. Fisher used the method of randomization in agricultural settings in the 1920s, the first report of an RCT in medicine was not published until 1948 (''Streptomycin treatment of pulmonary tuberculosis'') [1]. It was quickly recognized that the RCT would be useful in providing valid estimates of the average benefits of treatment in groups of patients. For the regulator interested in licensing pharmaceuticals and for the company interested in developing them, these average estimates proved acceptable [2]. Indeed, RCTs used for this purpose have been superb in separating useful from useless drugs and have enabled the development and approval of numerous medicines that have transformed patient care.

It is important to celebrate this accomplishment. During the past several decades, new therapies have led to effective control of risk factors for myocardial infarction and stroke; transformed HIV infection from a rapidly fatal disease to a chronic illness; cured Hepatitis C and achieved substantial improvements in the outcomes of some cancers. Many more advances in clinical therapeutics also owe their success to the findings that emerged from well-designed trials assessing the efficacy of new medicines.

Even these accomplishments of RCTs in drug approval have been tarnished by disappointments. Since the 1990s, over 20 medicines approved by regulators on the basis of valid, well-designed and appropriately implemented RCTs have later been withdrawn from use in clinical practice, and many others have been associated with adverse complications that were unrecognized in the preapproval studies [3]. Among the drugs withdrawn were well-known medicines like Vioxx (Rofecoxib) that was associated with an increase in cardiovascular risk and Rezulin (Troglitazone) that caused life-threatening liver failure. These errors in

* Corresponding author. Tel.: (215)707-5671; fax: (215)707-8431.
E-mail address: Ralph.horwitz@temple.edu (R.I. Horwitz).

http://dx.doi.org/10.1016/j.jclinepi.2017.02.003
0895-4356/

What is new?

- Despite the success of evidence-based medicine in strengthening the scientific basis of population medicine, EBM has been less successful in answering the physician's question: What is the best treatment for my particular patient? Medicine Based Evidence will build an archive individual patient profiles to provide the evidential base to guide clinical decision making in the personalized care of patients.

drug approval are not accidental. They are embedded in the design of trials that (1) test the efficacy of drugs in younger patients only to observe adverse effects in older patients; (2) test the effectiveness of drugs in trials that employ short-term follow-up when the medicine is intended to be used for much longer durations; or (3) report commonly occurring adverse effects but are unable to detect uncommon side effects even in trials with large sample sizes.

As serious as these shortcomings are in the use of RCTs as the foundation for EBM in drug development, there are even more profound shortcomings of EBM for the practice of Medicine. Most notably, EBM did not have a focus on evidence needed to guide decision-making about management of an individual patient.

2. EBMs greatest failures

The practice of medicine is complex. Clinical care is not directed toward groups of patients but to an individual patient whose biology and biography (social, behavioral, and environmental experiences) are distinctive, and whose goals of therapy are often at odds with the goals of EBM.

Because EBM relies so heavily on data from RCTs, the data do not include many types of treatments or patients seen in clinical practice; the results show the efficacy of treatment for an ''average'' randomized patient, not those in subgroups formed by cogent clinical features such as severity of illness, comorbidity or other clinical nuances; or psychosocial features such as stress, allostasis, or neighborhood deprivation that are known to affect both risk for disease and response to treatment. Randomized trial data are also seldom available for issues that are prominent in clinical practice such as etiology, diagnosis, and prognosis of disease. Physicians who seek to provide counseling to patients or take their personal preferences into account or learn strategies for giving comfort or reassurance to patients will find little help from the literature of EBM.

In the sections that follow, we describe some of the most prominent concerns about EBM and suggest how to develop a new approach to evidence for personalized care in clinical medicine.

3. EBM disregards lack of applicability of RCT results in clinical practice

RCTs are carried out in highly selected patients who are required to meet inclusion and exclusion criteria that often omit many of the patients who would later be candidates for treatment. Many trials impose restrictions on eligible patients who are judged to be too old or too young, to have illness that is too severe or not severe enough, or who have comorbidities that are common in patients with the main disease being treated. Recent reviews of trials that evaluated the benefits of statins and nonsteroidal anti-inflammatory drugs reported that women, older adults, and minorities were underrepresented [4].

Studies of the medicine montelukast for treatment of asthma illustrate the limits of EBM as currently practiced. Numerous RCTs of the asthma drug montelukast had shown that it was inferior to inhaled corticosteroids as a first-line treatment for asthma control and also inferior to long-acting beta agonists (LABAs) as a second-line ''add-on'' therapy. Montelukast is an oral medicine with higher adherence than that of inhaled agents when used in real-world settings. However, as often occurs in short-term (~6 months), placebo-controlled trials, patients maintain high levels of adherence within the trial that are not achievable outside the trial.

A study that illustrates the apparent advantage of inhaled steroids and LABAs comes from the results of an RCT in which montelukast was compared with beclomethasone and placebo. In this study, both montelukast and beclomethasone were superior to placebo [in improvements in forced expiratory volume in 1 second (FEV1)], and beclomethasone was superior to montelukast [5]. Despite these findings, montelukast remains popular with patients and physicians. Evidence to support the wisdom of this popularity was observed when montelukast was tested in real-world effectiveness studies. In these real-world studies, montelukast was just as effective as both inhaled corticosteroids and LABAs. What was different? [6].

The real-world studies enrolled patients with asthma who were more like those seen in actual clinical practice; had lower adherence rates that reflect levels seen commonly in customary care, not those artificially achieved in placebo-controlled trials; and measured clinical outcomes such as symptoms, function, and well-being. When discussing the results of their real-world trial, the authors noted that they deliberately included patients typically excluded in most EBM RCTs including those who smoke and those with coexisting conditions, poor adherence, or poor inhaler technique.

If there are serious concerns about the applicability of RCTs to real-world effectiveness, there is even greater concern that EBM fails to generate applicable evidence on the harms of treatment. RCTs are designed with sample sizes large enough to detect clinical benefits but not large enough to identify less commonly occurring potential