

ESSAY REVIEW

Tarnished Gold: The Sickness of Evidence-based Medicine by Steve Hickey and Hilary Roberts: EBM as an Avatar of Modern Medicine

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Abstract

Despite many passing references to contemporary frontiers of thought such as cybernetics and complexity theory, *Tarnished Gold*, a self-published book, leads the reader towards critical visions of clinical research enterprise that are more linked to the past than to the present or the future. Along the way, Evidence-Based Medicine is taken as the enemy, but is consistently misrepresented. The authors are seriously under-informed regarding contemporary issues and controversies related to the design of clinical research as well as the cognitive aspects of clinical practice. They ignore the relevance of narrative and relationship-centered medicine to those issues and controversies. The actual challenges of healthcare in our time and its relationship to clinical research are largely avoided. As a result, “*Tarnished Gold*” fails to illuminate or inform lessons already learned from the controversies that have occurred since the appearance of EBM. More importantly, the authors fail to observe that the terms of the debate between EBM and its critics have changed in the direction of an integrative approach, based on considerations of not only the logic of scientific inference, but of contemporary understanding of clinical reasoning and of the forms of knowledge that underlie it. Some of those terms are addressed by this review.

Keywords

Clinical epidemiology, clinical practice guidelines, clinical reasoning, clinical recommendations, Cochrane collaboration, evidence-based medicine, hierarchy of evidence, meta-analyses, modern medicine, person-centered medicine, positivism, randomized controlled trials, scientific inference, statistical effect sizes, subgroup analysis, systematic reviews

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“One would be remiss to say that EBM and its practice is a product of physicians alone. Technology has had a large role in the advancement of EBM” [1].

Introduction

“*Tarnished Gold*” [2] is a book authored by Steve Hickey and Hilary Roberts, two PhD’s who otherwise have co-authored and published numerous volumes espousing the healing properties of Vitamin C. It is ostensibly dedicated to discrediting errors and follies attributed by the authors to “evidence-based medicine” (EBM). The back cover of the paperback concludes with a regretful statement:

“It is time for medical practitioners to discard EBM’s tarnished gold standard, reclaim their clinical autonomy and provide individualized treatments to patients.”

Tarnished Gold (TG) is self-published and we presume the above statement to have been crafted or at least approved by, the authors themselves. It lends an initial undercurrent of nostalgia to the text, even as the book itself wanders through complex and disconnected pathways. Despite many passing references to contemporary frontiers of thought such as cybernetics and complexity theory,

Hickey and Roberts’ dissertation ultimately leads the reader more towards visions of the past than of the future. The actual challenges of healthcare in our time and its relationship to clinical research are largely avoided.

Reading *Tarnished Gold* (TG) is a bewildering experience. A passionate polemic against EBM is pursued obsessively throughout the volume. However, the reader rapidly discovers that the authors have an extremely superficial acquaintance with the literature and institutions of EBM. They refer several times to “The Cochrane Foundation”, apparently referring to the well known Cochrane Collaboration and its work to assemble electronically accessible databases of trials, systematic reviews and health services research. A reader with even casual familiarity with the EBM literature rapidly becomes aware that the representations of EBM within TG are grossly distorted and begins to suspect that this is not a volume about EBM at all. Rather, EBM is being used by Hickey and Roberts as a convenient ‘whipping boy’ for the purpose of advancing a deeper, anti-establishment, agenda. The ‘establishment’ in this case is the prevailing

framework of biomedical research - both basic and clinical - and its relationship to healthcare. The actual agenda of TG appears to emerge towards the end, as the content turns in the direction of a topic otherwise dear to its authors: the healing powers of vitamin C and the alleged suppression of recognition of those powers by the research enterprise that is EBM. Significantly, one individual identified by the TG authors as an adversary of research on megadose vitamin C as a treatment for paralytic poliomyelitis is Albert Sabin, the developer of the oral polio vaccine, the global administration of which has all but eradicated the disease worldwide [3]. Hickey and Roberts do not mention this. We cannot avoid noticing their emphasis, in their *Acknowledgement* section, on liaisons with the British Society for Ecological Medicine, an organization whose website home page conspicuously features links to articles warning of the dangers of immunizations [4].

Agenda notwithstanding, as an anti-establishment critique of today's biomedical research enterprise, *Tarnished Gold* is unsatisfying. It consistently not only misrepresents EBM, but also is seriously under-informed regarding the contemporary issues and controversies about the design of clinical research, the cognitive aspects of clinical practice and the relevance of narrative and relationship-centered medicine to those issues and controversies. The authors furthermore fail to address the content of the extensive literature of debate regarding EBM or of the content of the many published critiques that have appeared in the pages of the *Journal of Evaluation of Clinical Practice* and of other major medical journals, in the course of the 20 years since EBM appeared on the scene.

Given the misguided and agenda-ridden character of *Tarnished Gold* and the fact that it is certainly destined to have an extremely limited impact, is it a waste of time to review and discuss it? By touching upon a broad spectrum of issues related to healthcare and delivery, including foundational issues of biomedical science, albeit in an amateurish and superficial manner, Hickey and Roberts' book addresses the scope of the dilemma that health practitioners and their patients face, in very practical ways, on a day to day basis. The fact that they have selected EBM as the embodiment of evil within the citadel that they, for their own reasons, feel impelled to assault, is also salient. For these reasons, we believe it useful to use TG, including its misconceptions and distortions, as vehicles for outlining a truly contemporary and constructive approach.

"Ready, Fire, Aim": Who is the enemy?

Tarnished Gold, even as it initiates a relentless diatribe against EBM as 'the enemy', reflects an inconsistent and ever changing interpretation of the origin and nature of the adversary. In the early pages of the book, Hickey and Roberts commit themselves to a published definition of evidence-based medicine framed in terms of the context of individual patient care:

"Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [5].

Earlier in the chapter, the authors attribute the origins of EBM to the discipline of clinical epidemiology [6]. Shortly thereafter, the authors suggest that EBM is largely a pawn of "corporate medicine, governments and the medical establishment." Still earlier, in the preface to TG, the authors have suggested that "EBM ...developed from organized medicine". Returning to the first chapter, the TG authors assert that "...the origins of EBM lie in the legal system." This is apparently based on little more than the observation that information from research, defined as "evidence" and the concept that some evidence is admissible and some not, bears some resemblance to the use of the term "evidence" in judicial proceedings. In other contexts not noted by the authors of TG, the origins of EBM have been attributed to the results of variations research [7,8].

Is there a "true" historical attribution of the evils (if you are an adversary) or the fruits (if you are an advocate) of EBM? We, based on over 15 years of close collaboration with founders of the EBM movement, previously provided a critical history of EBM [9] as it was officially formulated in 1992 [10]. That formulation pertained to teaching and practice regarding the care of individual patients and led to incorporation of much of the content to be found in standard EBM texts into curricula of competency-based graduation medical education [11]. However, the term "EBM" also disseminated with lightning speed to encompass many additional dimensions [7,12]. Furthermore, the phrase "evidence-based" had already been interjected into the medical literature in the context of criteria for clinical practice guidelines, a context extending beyond that of care of individual patients [13]. Hence, the issue of the relationship of healthcare policy to scientific evidence was already on the table at the point that the term "evidence-based medicine" was put forward in the pages of a major medical journal as a "new paradigm of teaching and practice of medicine" [10].

To summarize, over the course of over 40 years since Sackett and Feinstein individually developed the science of clinical epidemiology [6,14] the need to integrate information from clinical and health services research into clinical policy and practice has become part of the fabric of the healthcare system, from the level of national healthcare regulation, all the way down to that of the training of clinicians in all disciplines. This has been driven throughout by the ever expanding explosion of published research [9,15] and of universal electronic access to such information. Hence, "EBM", once a new buzz term affixed to an over-reaching educational initiative [10], no longer constitutes a well-defined or compelling target of dissent. Efforts to make it such, begin to call up images of a bygone era. Much more salient is the recognition that many of the major challenges facing healthcare in our time revolve around issues which relate to the imperative to integrate the worlds of scientific research and healthcare delivery, healthcare policy, the care of individual patients and the science and the art of clinical medicine. The

authors of *Tarnished Gold* appear oblivious to these challenges as they march inevitably towards their apparent goal, exemplified by the championing of potential effectiveness of megadoses of vitamins in the treatment of an infectious disease that no longer exists.

The EBM Wars

Vehement as is *Tarnished Gold* in its critique of EBM, the authors appear largely oblivious to the literature of dissent to which one might expect them to have been drawn. The initial advocates of “EBM”, as a prescription for teaching clinical medicine, aroused great ire within the medical literature, not because they suggested that literacy in reading and interpreting clinical research was a useful point of emphasis in the education of physicians, but because, referring to the writings of Thomas Kuhn [16], they also claimed to be defining a ‘new paradigm’ for the teaching and practice of medicine [10]. This claim was rapidly recognized to be both mistaken and potentially dangerous. The often cited 1992 ‘manifesto’ [10] was framed from a narrow, epidemiologically weighted, perspective. Posed as a “new paradigm”, the suggestion that consideration of clinical research is routinely relevant to clinical decision-making, was widely interpreted as an assault on the integrity and importance of many dimensions of clinical expertise that require a lifetime to master [17]. New disciplines such as narrative medicine [18] had emerged to address these dimensions. EBM advocates soon acknowledged that consideration of patient values and preferences - and of practice context and clinical circumstances - not only of information from clinical research, are needed informants of clinical decision-making [19-21]. However, neither in those sources, nor in subsequent EBM literature, have products and tools been developed that offer an integrated solution to the challenge to practice posed by the explosion of research information [9,22,23]. Rather, the debate itself has served to illuminate crucial dimensions of the problem and, most importantly, the level upon which its solution must be sought. These include the necessary relationship between the design and interpretation of clinical research and foundational medical knowledge [24], the necessarily indirect relevance of research performed on populations to the care of individual patients [25] and even the need to reconceptualize the prevailing foundational model of medicine [26]. Locating the proper position of information from clinical research within a unifying and adequate epistemological hierarchy constitutes an essential aspect of the problem and its solution. Illustrating the role of EBM advocacy in motivating critical dialogue, a recent, weak attempt by some of the original proponents of EBM at addressing philosophical challenges to EBM as a ‘paradigm’ [27], led to an even more systematic reflection on the part of ourselves and others such as Miles on essential issues affecting conceptual integration [23,28].

Hickey and Roberts, if they are aware of the substance of this 20 year long debate, largely ignore it in the course of pursuing their own critique. They stress the importance

of what they call “the ecological fallacy”, that is, the failure to distinguish between population averages drawn from clinical research and the direct likelihood of an outcome within a single individual. However, rather than exploring the implications of this dilemma in depth, they use it as a pretext for virtually dismissing the relevance of clinical research as currently performed and published to practice. They cryptically label EBM as a manifestation of a social constructivist outlook [29], overlooking the self-labeling of EBM by its originators as positivist [27], a label with which we concur [23]. Most importantly, Hickey and Roberts fail to observe that the terms of the debate between EBM and its critics have changed considerably over recent years.

Although EBM advocates may have brought little new to the debate in recent years, the tone of much of the criticism has shifted away from the polarization of the 90’s in favor of a more concerted quest for conceptual resolution. Sehon *et al* [30] observed that EBM’s claim to represent a scientific revolution was unsupported by its content, which essentially amounted to no more than a prescription for wise use of information from clinical research to guide practice. They suggest that the holistic approach of Quine allows escape from the constraints of positivism. Although not directly addressing the relational and narrative realm within which living patients are to be recognized as *persons*, Sehon *et al.* suggest the existence of a continuum within which patients’ and practitioners’ experience and evidence from randomized trials, can be regarded as essential ingredients of healthcare actions. More recently, the need for conceptual and epistemological integration has begun to appear in critical writings regarding EBM [31,32]. Our own inquiries [23] lead us beyond the pragmatism of Quine and to the relevance of constructivism as embodied in the writings of Freire [33]. This notion of social constructivism has nothing to do with the lapse into subjectivism characteristic of constructivist writings cited by Hickey and Roberts. We [23] and others [34], perceive that potential solutions to the dilemma posed by Cartesian dualism may be found in complexity theory [35]. It is within this domain that the dichotomies between verificationism and realism, that is, the “science” *versus* the “art” of medicine, seem most fruitfully sought. From this perspective, although EBM appears largely trapped within the past, it nonetheless appears less and less an important culprit. Far from defining the goal of integrated practice, EBM helps illuminate the path through which the actual goal may be pursued in a fashion that addresses the complexity of 21st Century healthcare. The most important weakness of TG is, perhaps, that it is tangential to today’s issues. We will confine the rest of our discussion to themes that appear most pertinent to those issues.

EBM and the Research Enterprise

Throughout *Tarnished Gold*, the authors refer to EBM and to the industry-dominated sector of the clinical research enterprise, interchangeably. If the EBM literature constituted an uncritical endorsement of clinical trials,

such an equation might be justified. After all, only a few years ago, Richard Horton, Editor of *The Lancet*, reviewing a book by Sheldon Krinsky [36], proclaimed that “Journals have devolved into information-launders operations for the pharmaceutical industry” [37]. His sentiments were echoed by the former Editor of the *British Medical Journal* [38]. Missed by Hickey and Roberts is that the founders and advocates of EBM have consistently been in the forefront of efforts to immunize healthcare professionals against the effects of industry-related subterfuge [39]. Furthermore, EBM founders and advocates have rigorously illuminated sources of researcher bias previously unappreciated even in academic quarters and they have done this in ways that reach out to clinicians and educators. Examples include the misuse of composite endpoints, in which clinically trivial outcomes that occur frequently are summed with rarely occurring major outcomes in a fashion that falsely inflates the clinical importance of trial results [40]; erroneous approaches to subgroup analysis [41]; demonstrations of the magnitude of inflation of trial effects when trials are stopped early for benefit [42] and the subterfuge embodied in the emphasis on *relative* rather than *absolute* measures of effect [43].

Hickey and Roberts advance warnings regarding the premature stopping of clinical trials and the statistical significance of clinically insignificant effects as ‘evidence’ in support of their anti-EBM discourse [2]. They make no mention of the role of EBM founders and advocates in providing professional readers and educators with well-researched demonstrations and tools aimed at exposing and neutralizing these very subterfuges. Has EBM, through its emphasis on randomized trials and despite extensive efforts to expose the methods of researcher and marketing bias, ultimately served to advance proprietary interests? Whatever future historians may conclude, the answer to this question is vastly more complex than the authors of TG seem prepared to deal with. To the extent to which they are genuinely concerned about the corruption of research by proprietary interests, they appear to us to have overlooked an important ally in the course of their focus on EBM as the adversary of science.

Related to the nature of EBM and ‘establishment’ interests and biases, the TG authors express concern with overuse of technology and blind endorsement of screening [2]. Again, they fail to acknowledge EBM as their allies in these concerns. The 2009 revised recommendations for breast cancer screening in younger women [44], based on a systematic review of trial evidence [45], unleashed an outcry of political protest in the United States [46]. Dissenters from the limited screening recommendations included right wing politicians, stakeholders within medical imaging specialties and patient advocacy groups. This demonstrated a very different alignment between establishment interests and EBM methodology than that portrayed by Hickey and Roberts.

RCTs, clinical practice and policy

EBM has been a users’ and consumers’ movement in healthcare. EBM does not produce research, as frequently implied by Hickey and Roberts. Rather, it summarizes and appraises it and develops recommendations based upon the assessment of quality and the magnitude of the results of studies. However, in one sense, Hickey and Roberts are correct in their assertion of an alignment between EBM and research. The principle of a hierarchy of study designs, with randomized controlled trials (RCTs) at the top of the pyramid for most research questions, is central to the methodology of EBM. When certain specifications regarding component studies are fulfilled, meta-analysis may further increase the precision of estimates of effect and of other outcomes [47]. Hickey and Roberts take vehement issue with the hegemony of RCTs within the evidence hierarchy and are, if possible, even more strident when it comes to denouncing meta-analysis [2]. The two issues are closely related. Meta-analyses may be performed in a fashion that includes any category of study design. However, meta-analyses of randomized trials of treatment and prevention are particularly prominent in the literature and - until recently - were the sole product of the Cochrane Collaboration.

The TG authors’ objections to meta-analyses and systematic reviews of treatment are largely based on the exclusion by those analytical designs of observational studies. However, Hickey and Roberts also point to the attempt to locate and include unpublished data in systematic reviews, a required reporting element within the PRISMA guideline [48], compliance with which is required by most major journals as a condition for acceptance of such a review for publication. Once again, they appear seriously uninformed with respect to the EBM and methodological literature. They fail to mention that failure to include unpublished data in a meta-analysis may result in dangerous over-estimation of treatment effects due to withholding of negative trials from publication by pharmaceutical sponsors. Examples of this in the area of medications for psychiatric illnesses have recently attracted major attention [49-51]. Such “reporting bias” leads to over prescribing of expensive drug therapy and unwarranted exposure of patients to adverse effects of medicines. Susceptibility to publication bias is stressed as a key factor in evaluating the quality of systematic reviews in the EBM literature [52].

The notion that EBM overemphasizes the importance of RCTs to the exclusion of evidence from other types of research furthermore is not new [9]. Such views have been voiced frequently over the years, including from illustrious sources [53,54]. Hickey and Roberts couch their opposition to emphasis on RCTs in a novel fashion. They challenge the premises of statistical inference that form the basis of how trial data is conventionally reported and counterpose their own account of Bayesian statistical methods [2]. Much of their discussion of statistical issues is arcane. However, their description of a “Bayesian trial” that a practitioner might do for himself to determine the apparent effectiveness of a therapy among his own patients is of

some interest. It corresponds to what is being called “practice-based research” [55]. Here is yet another example of the TG authors looking blindly backwards, rather than to the frontiers of today’s healthcare environment. They make no mention of the concept of comparative effectiveness research (CER) [56,57], a development that is moving clinical research away from exclusive emphasis on trials of efficacy performed under research conditions and towards the issue of what actually works in real world practice. The concept of a strictly controlled trial with tight inclusion criteria is being challenged by that of a pragmatic trial, designed to simulate real world conditions and to carry greater relevance to healthcare decisions [58,59]. However, the implications of the CER movement go far beyond the design of randomized trials. Interventions characterized by the inherent need for patient preference and participation may be incompatible with a randomized design [60-62]. Related to CER, still another dimension of research has recently emerged. Called “patient-oriented research”, it seeks directly to engage patients themselves in the clinical research enterprise, as co-designers and advisors of study design [63].

Within the framework of evidence-based guidelines, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, incorporates a principle of equity, based on methodological criteria, of observational studies in relationship to randomized trials [64,65]. Randomized trials of poor quality may be rated lower and observational studies of high quality may be rated higher, breaking the rigidity of the classical EBM hierarchy of evidence. Importantly the architects of the GRADE system include some of the prominent founders of the EBM movement. Furthermore, new guidelines for systematic reviews of CER explicitly call for inclusion of observational studies in addition to randomized trials [47]. Still further, sophisticated challenges, coupled with innovative approaches to the ability of evidence-based guidelines to effectively predict benefit for individual patients, are being advanced by some of the founders of the very concept of such guidelines [66].

These modifications to the traditional EBM formula are transformative. They reflect the advent of a new era of clinical research in which at least two kinds of information from empirical studies are required for a clinical option to be fully evaluated. Information regarding real world effectiveness is essential to patients, practitioners and policymakers. At the same time, scientists and policymakers continue to need direct evidence of efficacy of interventions under research conditions. Such evidence reinforces confidence that those interventions’ intrinsic (as opposed to placebo) effects justify commitments of public resources, illuminate issues of mechanism of action that may inform or modify underlying pathophysiological hypotheses. For full implementation within a particular practice setting, still an additional type of information is required, derived from one’s own practice experience [67].

Hickey and Roberts appear entirely oblivious to these concepts, issues and developments. Our summary of them is not to be interpreted as a blanket defense of EBM in these respects. Mainstream EBM may constitute a

traditional and conservative force in these domains. Some leading EBM proponents resist the importance of pragmatic clinical trials and observational evidence of real world effectiveness [68]. Even as it finds itself bending under the winds of change within the healthcare system, EBM is no longer the major source of disturbing provocation that it once was and may now, sometimes, constitute a voice of opposition to such provocations. A *valid* critique of the role of EBM in our time therefore requires attention to the current realities of healthcare, to the actual frontiers of research design and application and to the historical development of the relevant ideas and debates over the past 30 years. Tarnished Gold falls notably short on all of these counts.

Scientific inference and clinical reasoning

Several additional aspects of Hickey and Roberts’ wandering dissertation are worthy of brief note for the purpose of clarifying issues important to the contemporary evolution of healthcare. One of these has to do with the way that conclusions relevant to practice are drawn from a research report. For unclear reasons, perhaps motivated by the desire to discredit hypothesis driven trial design, the TG authors assert that “science is induction.” Quoting Ronald Fisher, Hickey and Roberts suggest that induction, in contrast to deduction, is the only valid scientific process through which new knowledge can be generated. They argue that induction, which derives theories through accumulation and synthesis of information from experience, is hypothesis generating, whereas deduction is limited to the testing of hypotheses. Not mentioned by Hickey and Roberts is the more complex and salient concept of “abductive reasoning”, developed over 130 years ago by Charles Sanders Peirce [69], perhaps the founding father of modern clinical research methodology and inference.

Peirce’s notion of abductive reasoning, much more than the notions of pure induction or pure deduction, encompasses the process through which empirical observations result in the perception of patterns of relationship and consequently hypotheses, which are then subjected to empirical testing. Such reasoning happens through self-organizing cognitive processes, on both conscious and tacit levels. Hypotheses can only be refuted, not conclusively affirmed [70]. Refutation of hypotheses through rigorous empirical research then may result in appropriate challenges to the validity of the originally perceived patterns as well as of the premises upon which the corresponding hypotheses were formulated. Hence, “refutationism” [70] informs new and revised hypotheses regarding effectiveness and mechanisms of action. This is how scientific knowledge, mediated through informed social process, advances.

At stake in this issue is the concept of a lawful interplay between foundational medical theory and understanding of empirical observations of real patients experiencing or avoiding important clinical outcomes

under current circumstances of healthcare delivery. This interplay between rigorous efficacy trials, grass roots observational studies and basic science investigations, informed by practice-based research, is consistent with the germinal concepts of Peirce, but avoided by the linear dichotomies posited by Hickey and Roberts.

Hickey and Roberts' attempts to address the process of clinical reasoning on the part of an individual practitioner in his/her response to an individual patient are uninformed. What they, as individuals who are neither clinicians nor close to clinical medicine fail to acknowledge, is the tacit dimension of clinical cognition. Research on medical cognition is not new. Leading currents in cognitive psychology and its relationship to the development of clinical expertise have recognized that clinical problem-solving and decision-making is complex and involves both inductive and deductive components [71,72], as well as differentiated cognitive structures termed "illness scripts" [72]. The latter reflect self-organizing processes commensurate with complexity theory, a domain to which the TG authors give credence, but to which they do little justice in the course of their denunciations of a single source of evil in healthcare: "EBM".

Conclusion

EBM began as a useful provocation, it became an ubiquitous and universally appealing 'buzz term' and marketing label and now has become a conservative influence on issues of research design in healthcare, even as its novelty fades into medical history. Diatribes against EBM usefully informed the process that was unleashed by its appearance and ironically increased its value by helping to clarify the issues. Such diatribes today only serve to propel us into the past and to engage us with yesterday's news. Aside from many useful approaches to the evaluation of clinical research, the valuable lessons to be learned from EBM are those to be distilled from the process that unfolded in the wake of its release. We conclude that Tarnished Gold fails to illuminate or inform such lessons.

References

- [1] Claridge, J.A. & Fabian, T.C. (2005). History and development of evidence-based medicine. *World Journal of Surgery* 29, 547-553.
- [2] Hickey, S. & Roberts, H. (2011). Tarnished Gold: The Sickness of Evidence-based Medicine.
- [3] Global Polio Eradication Initiative. <http://www.polioeradication.org/>. Accessed March 17, 2012.
- [4] British Society for Ecological Medicine. <http://www.ecomed.org.uk/>. Accessed March 17, 2012.
- [5] Sackett, D.L., Rosenberg, W.M., Gray, J.A., Haynes, R.B. & Richardson, W.S. (1996). Evidence based medicine: what it is and what it isn't. *British Medical Journal* 312, 71-72.
- [6] Sackett, D.L., Haynes, R.B. & Tugwell, P. (1985). *Clinical Epidemiology*. Boston: Little, Brown and Company.
- [7] Eddy, D.M. (2005). Evidence-based medicine: A unified approach. *Health Affairs* 24, 9-17.
- [8] Wennberg, J. & Gittelsohn, A. (1973). Small Area Variations in Health Care Delivery. *Science* 182, 1102-1111.
- [9] Wyer, P.C. & Silva, S.A. (2009). Where Is The Wisdom: I. A Conceptual History of Evidence Based Medicine *Journal of Evaluation in Clinical Practice* 15, 891-898.
- [10] Evidence-Based Medicine Working Group. (1992). Evidence-based medicine: A new approach to teaching the practice of medicine. *Journal of the American Medical Association* 268, 2420-2425.
- [11] Nasca, T.J., Philibert, I., Brigham, T. & Flynn, T.C. (2012). The Next GME Accreditation System - Rationale and Benefits. *New England Journal of Medicine* 366, 1051-1056.
- [12] Charlton, B.G. & Miles, A. (1998). The rise and fall of EBM. *Quarterly Journal of Medicine* 91, 371-374.
- [13] Eddy, D.M. (1990). Practice policies: Where do they come from? *Journal of the American Medical Association* 263, 1266-1275.
- [14] Feinstein, A.R. (1968). Clinical epidemiology I. The populational experiments of nature and of man in human illness. *Annals of Internal Medicine* 69, 807-820.
- [15] Bastian, H., Glasziou, P. & Chalmers, I. (2010). Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up? *PLoS Med* 7, e1000326.
- [16] Kuhn, T.S. (1962). *The Structure of Scientific Revolutions*. Chicago: University of Chicago Press.
- [17] Tanenbaum, S.J. (1993). What Physicians Know. *New England Journal of Medicine* 329, 1268-1271.
- [18] Charon, R. (2001). Narrative Medicine: A model for empathy, reflection, profession, and trust. *Journal of the American Medical Association* 286, 1897-1902.
- [19] Haynes, R.B., Devereaux, P.J. & Guyatt, G.H. (2002). Physicians' and patients' choices in evidence based practice: Evidence does not make decisions, people do. *British Medical Journal* 324 (7350) 1350.
- [20] Haynes, R.B., Devereaux, P.J. & Guyatt, G.H. (2002). Clinical expertise in the era of evidence-based medicine and patient choice. *American College of Physicians Journal Club* 136, A11-A14.
- [21] Haynes, R.B., Sackett, D.L., Gray, J.R., Cook, D.C. & Guyatt, G.H. (1996). Transferring evidence from research into practice: 1. The role of clinical care research evidence in clinical decisions [Editorial]. *American College of Physicians Journal Club* 125, A14-A16.
- [22] Charles, C., Gafni, A. & Freeman, E. (2010). The evidence-based medicine model of clinical practice: scientific teaching or belief-based preaching? *Journal of Evaluation in Clinical Practice* 17, 597-605.
- [23] Silva, S.A. & Wyer, P.C. (2009). Where is the wisdom? II - Evidence-based medicine and the epistemological crisis in clinical medicine. Exposition and commentary on Djulbegovic, B., Guyatt, G. H. & Ashcroft,

- R. E. (2009) *Cancer Control* 16, 158–168. *Journal of Evaluation in Clinical Practice* 15, 899-906.
- [24] Tonelli, M.R. & Callahan, T.C. (2001). Why Alternative Medicine Cannot Be Evidence-based. *Academic Medicine* 76, 1213-1220.
- [25] Tonelli, M.R. (1998). The philosophical limits of evidence-based medicine. *Academic Medicine* 73, 1234-1240.
- [26] Malterud, K. (1995). The legitimacy of clinical knowledge: Towards a medical epistemology embracing the art of medicine. *Theoretical Medicine and Bioethics* 16 (2) 183-198.
- [27] Djulbegovic, B., Guyatt, G.H. & Ashcroft, R.E. (2009). Epistemologic Inquiries in Evidence-Based Medicine. *Cancer Control* 16, 158-168.
- [28] Miles, A. (2009). Evidence-based medicine: requiescat in pace? A commentary on Djulbegovic, B., Guyatt, G. H. & Ashcroft, R. E. (2009) *Cancer Control* 16, 158–168. *Journal of Evaluation in Clinical Practice* 15, 924-929.
- [29] Brown, P. (1995). Naming and Framing: The Social Construction of Diagnosis and Illness. *Journal of Health and Social Behavior* 35 (Supplement) 34-52.
- [30] Sehon, S.R. & Stanley, D.E. (2003). A philosophical analysis of the evidence-based medicine debate. *BMC Health Services Research* 3, 14.
- [31] Miles, A. & Loughlin, M. (2011). Models in the balance: evidence-based medicine versus evidence-informed individualized care. *Journal of Evaluation in Clinical Practice* 17, 531-536.
- [32] Miles, A. & Mezzich, J.E. (2012). The care of the patient and the soul of the clinic: person-centered medicine as an emergent model of modern clinical practice. *International Journal of Person Centered Medicine* 1 (2) 207-222.
- [33] Freire, P. (1974). *Education for Critical Consciousness*. New York: Continuum.
- [34] Greenhalgh, T. & Russell, J. (2006). Promoting the Skills of Knowledge Translation in an Online Master of Science Course in Primary Health Care. *Journal of Continuing Education in the Health Professions* 26, 100-108.
- [35] Varela, F.J., Thompson, E. & Rosch, E. (1991). *The Embodied Mind*. Cambridge, MA: MIT.
- [36] Krimsky, S. (2004). *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* Lanham, MD: Rowman and Littlefield.
- [37] Horton, R. (2004). The Dawn of McScience. *New York Review of Books* 51, 7-9.
- [38] Smith, R. (2005). Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies. *PLoS Medicine* 2, e138.
- [39] Montori, V.M., Jaeschke, R., Schunemann, H.J., Bhandari, M., Brozek, J.L., Devereaux, P.J. & Guyatt, G.H. (2004). Users' guide to detecting misleading claims in clinical research reports. *British Medical Journal* 329 (7474) 1093-1096.
- [40] Montori, V.M., Permyer-Miralda, G., Ferreira-Gonzalez, I., Busse, J.W., Pacheco-Huergo, V., Bryant, D., Alonso, J., Akl, E.A., Domingo-Salvany, A., Mills, E. & Wu, P. (2005). Validity of composite end points in clinical trials. *British Medical Journal* 330 (7491) 594-596.
- [41] Wyer, P.C., Perera, P., Jin, Z., Zhou, Q., Cook, D.J., Walter, S.D. & Guyatt, G.H. (2006). Vasopressin or Epinephrine for Out-of-Hospital Cardiac Arrest. *Annals of Emergency Medicine* 48, 86-97.
- [42] Montori, V.M., Devereaux, P.J., Adhikari, N.K., Burns, K.E., Eggert, C.H., Briel, M., Laccetti, C., Leung, T.W., Darling, E., Bryant, D.M., Bucher, H.C., Schünemann, H.J., Meade, M.O., Cook, D.J., Erwin, P.J., Sood, A., Sood, R., Lo, B., Thompson, C.A., Zhou, Q., Mills, E. & Guyatt, G.H. (2005). Randomized trials stopped early for benefit: a systematic review. *Journal of the American Medical Association* 294 (17) 2203-2209.
- [43] Barratt, A., Wyer, P.C., Hatala, R., McGinn, T., Dans, A.L., Keitz, S., Moyer, V., For, G.G. & Evidence-Based Medicine Teaching Tips Working Group. (2004). Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. *Canadian Medical Association Journal* 171 (4) 353-358.
- [44] U.S. Preventive Services Task Force. (2009). Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine* 151, 716-726.
- [45] Nelson, H.D., Tyne, K., Naik, A., Bougatsos, C., Chan, B.K. & Humphrey, L. (2009). Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 151, 727-737.
- [46] Quanstrum, K.H. & Hayward, R.A. (2010). Lessons from the mammography wars. *New England Journal of Medicine* 363, 1076-1079.
- [47] Institute of Medicine. (2011). *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, D.C.: National Academies Press.
- [48] Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. & PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6 (7) e1000097.
- [49] Eyding, D., Lelgemann, M., Grouven, U., Härter, M., Kromp, M., Kaiser, T., Kerekes, M.F., Gerken, M. & Wieseler, B. (2010). Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *British Medical Journal* 341, c4737.
- [50] Loder, E. & Godlee, F. (2010). Missing clinical trial data: setting the record straight: Urgent action is needed to restore the integrity of the medical evidence base. *British Medical Journal* 341, 787-788.
- [51] Turner, E.H., Knoopfmacher, D. & Shapley, L. (2012). Publication Bias in Antipsychotic Trials: An Analysis of Efficacy Comparing the Published Literature to the US Food and Drug Administration Database. *PLoS Med*. 9 (3) e1001189.
- [52] Montori, V., Ioannidis, J. & Guyatt, G. (2008). *Advanced Topics in Systematic Reviews: Reporting Bias*. In: *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. 2nd edn. (Guyatt, G., Rennie, D., Meade, M.O. & Cook, D.J., eds.) pp. 543-554. NY: McGraw-Hill.

- [53] Feinstein, A.R. (1983). An Additional Basic Science for Clinical Medicine: II. The Limitations of Randomized Trials. *Annals of Internal Medicine* 83, 554-550.
- [54] Feinstein, A.R. & Horwitz, R.I. (1997). Problems in the "Evidence" of "Evidence-based Medicine" *American Journal of Medicine* 103, 529-535.
- [55] Westfall, J.M., Mold, J. & Fagnan, L. (2007). Practice-based research: "Blue Highways" on the NIH roadmap. *Journal of the American Medical Association* 297, 403-406.
- [56] Sox, H.C. (2009). Comparative effectiveness research: A report from the Institute of Medicine. *Annals of Internal Medicine* 151, 203-205.
- [57] Sox, H.C. (2010). Defining Comparative Effectiveness Research: The Importance of Getting It Right. *Medical Care* 48 (Supplement 1) S7-S8.
- [58] Oxman, A.D., Lombard, C., Treweek, S., Gagnier, J.J., Maclure, M. & Zwarenstein, M. (2009). Why we will remain pragmatists: four problems with the impractical mechanistic framework and a better solution. *Journal of Clinical Epidemiology* 62 (5) 485-488.
- [59] Ware, J.H. & Hamel, M.B. (2011). Pragmatic Trials — Guides to Better Patient Care? *New England Journal of Medicine* 364, 1685-1687.
- [60] Black, N. (1996). Why we need observational studies to evaluate the effectiveness of health care. *British Medical Journal* 312, 1215-1218.
- [61] Brewin, C.R. & Bradley, C. (1989). Patient preferences and randomized clinical trials. *British Medical Journal* 299, 313-315.
- [62] King, M., Nazareth, I., Lampe, F., Bower, P., Chandler, M., Morou, M., Sibbald, B. & Lai, R. (2005). Impact of participant and physician intervention preferences on randomized trials: a systematic review. *Journal of the American Medical Association* 293 (9) 1089-1099.
- [63] Clancy, C. & Collins, F.S. (2010). Patient-Centered Outcomes Research Institute: The Intersection of Science and Health Care. *Science Translational Medicine* 2 (37) 37cm18.
- [64] Guyatt, G.H., Oxman, A.D., Kunz, R., Vist, G.E., Falck-Ytter, Y. & Schünemann, H.J. (2008). What is "quality of evidence" and why is it important to clinicians? *British Medical Journal* 336, 995-998.
- [65] Guyatt, G.H., Oxman, A.D., Vist, G.E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H.J. & GRADE Working Group. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal* 336, 924-926.
- [66] Eddy, D.M., Adler, J., Patterson, B., Lucas, D., Smith, K.A. & Morris, M. (2011). Individualized guidelines: the potential for increasing quality and reducing costs. *Annals of Internal Medicine* 154, 627-634.
- [67] Frankovich, J., Longhurst, C.A. & Sutherland, S.M. (2011). Evidence-Based Medicine in the EMR Era. *New England Journal of Medicine* 365, 1758-1759.
- [68] Karanicolas, P.J., Montori, V.M., Devereaux, P.J., Schünemann, H., Guyatt, G.H. (2009). A new "Mechanistic-Practical" Framework for designing and interpreting randomized trials. *Journal of Clinical Epidemiology* 62, 479-484.
- [69] Peirce, C.S. (1878). Illustrations of the Logic of Science: Sixth Paper-Deduction, Induction and Hypothesis. *Popular Science Monthly* 13, 470-482.
- [70] Maclure, M. (1985). Popperian Refutation in Epidemiology. *American Journal of Epidemiology* 121, 343-350.
- [71] Norman, G. (2005). Research in clinical reasoning: past history and current trends. *Medical Education* 39, 418-427.
- [72] Schmidt, H.G., Norman, G.R. & Boshuizen, H.P.A. (1990). A Cognitive Perspective on Medical Expertise: Theory and Implications. *Academic Medicine* 65, 611-621.
- [73] Silva, S.A., Charon, R. & Wyer, P.C. (2011). The marriage of evidence and narrative: scientific nurturance within clinical practice. *Journal of Evaluation in Clinical Practice* 17, 585-593.
- [74] Epstein, R.M. & Peters, E. (2009). Beyond Information: Exploring Patient's Preferences. *Journal of the American Medical Association* 302, 195-197.
- [75] Barry, M.J. & Edgman-Levitan, S. (2012). Shared Decision Making: The Pinnacle of Patient-Centered Care. *New England Journal of Medicine* 366, 780-781.
- [76] Thaler, R.H. & Sunstein, C.R. (2003). Libertarian Paternalism. *American Economic Review* 93, 175-179.
- [77] Beach, M.C. & Inui, T. (2006). Relationship-centered Care: A Constructive Reframing. *Journal of General Internal Medicine* 21, S3-S8.