The Role of Evidence-Based Medicine in Rational Drug Use

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Introduction to Evidence-Based Medicine

Evidence-based medicine (EBM) remains a hot topic for clinical epidemiologists, clinicians, health planners, healthcare payers, and the public. "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. It involves the integration of individual clinical expertise with the best available external clinical evidence" (Sackett, et al., 1996).

Evidence-based medicine is best viewed as a process with several steps: identifying a clinical question; systematically searching for clinical studies that address this question; critically reviewing these studies to eliminate those that are poor quality or irrelevant, and interpreting the rest as best as possible; and then basing the answer to the question on those superior studies. Evidence-based medicine is well suited to address which treatment, including pharmaceutical treatments, might be best for a particular patient. Note that "the best" here means the treatment at an affordable cost, most likely to maximize benefits and minimize harms to the patient, allowing for how the patient values particular benefits, harms and health expenditure (Poses, 2006).

Clinical Expertise and EBM

Individual clinical expertise (the proficiency and clinical judgement acquired by experience) is reflected in effective and efficient diagnosis and in mindful identification and compassionate use of an individual patient's predicaments, rights, and preferences in making clinical decisions about his/her care. The best available external clinical evidence for rational therapy derives from clinically relevant research into the efficacy, effectiveness, and safety of therapeutic, rehabilitative, and preventive regimens (Sackett, et al., 1996).

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Rational Therapy and EBM

The essential principles of rational drug therapy that are taught in medical school, including physiology, pharmacokinetics, and pharmacodynamics, are all too easily forgotten and must be regularly reviewed. New drugs are appearing at a rapid rate, and an increasingly bewildering array of drug interactions exists. Moreover, post-marketing reports of adverse events occur almost daily. It's no surprise, then, that suboptimal prescribing practices are widespread (Donnell, 2006). Two examples: i) In a study of hospitalized patients taking metformin, 27% were given the drug despite at least one absolute contraindication (Calabrese, 2002); ii) Despite strong evidence to support the use of beta blockers and angiotensin-converting enzyme (ACE) inhibitors in heart failure, and anticoagulants for prevention of venous thromboembolism, these medications are prescribed at an inordinately low rate (Fanarow, 2005).

For rational decision making, a physician needs to apply his/her clinical expertise on the best available external evidence. At times, even the strongest external evidence may not be applicable to or appropriate for an individual patient and therefore an individualised intervention may have to be tried (N=1 trial). A physician without the clinical expertise can be tyrannized by evidence and risks practicing 'cook-book medicine'. On the other hand, even the most experienced clinical expert, who eschews the current scientific evidence, faces the risk of becoming out of date, to the detriment of patients (Sackett, et al., 1996). Rational approach and EBM complement each other quite well.

How EBM strategy fits into RDU strategy

How the strategies of EBM and rational therapy fit into the different stages of a clinical encounter is shown below:

Patient with symptoms and signs of an illness or a disease – (Apply clinical methods, pathophysiology & diagnostic methods for diagnosis)

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Management decisions in clinical uncertainty – (Use EBM if available or N=1 trial)

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Therapeutic decision – (Apply clinical pharmacology & principles of rational therapy)

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Individualize therapy – (Incorporate patient's beliefs & preferences; utilize pharmacogenomics if available)

↓

Monitor response – (Mindful watch for adverse events)

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Closure of the clinical consultation

It is clear that the goal of EBM is quite concordant with the goal aim of rational therapy, i.e., to promote better patient care through safe and effective (drug) therapy. EBM makes available relevant therapeutic information based on the best available evidence that can guide prescribers to prescribe rationally.

Shifting Evidence from Bench to Bedside

The scientific evidence generated by medical research is often not incorporated into clinical practice in a timely and dependable manner. Some of the well-documented beneficial therapies in the 90s were utilized in only <30% of eligible patients; examples include: influenza vaccination, aspirin and beta-blockers after myocardial infarction, and angiotensin converting enzyme inhibitors for reduced ventricular function or diabetic nephropathy. Other therapies that have been proven ineffective or harmful continue to be utilized. Studies have also documented the problems and costs associated with drug misadventures and adverse drug events as a result of not following the current best practice (Moores, 1997).

The documentation of suboptimal and widely variable therapeutic care casts doubt on the knowledge base or decision-making process or both. Access to properly formatted, systematically collected, and synthesized evidence will improve the decision-making process, reduce unnecessary variability in the provision of care, and improve the overall quality and outcomes of care (ibid). A study of the impact of EBM guidelines has shown that explicit

guidelines, when introduced in the context of rigorous evaluation, improve clinical practice. However, the size of the improvements in performance varied considerably (Grimshaw & Russell, 1993).

Problems with EBM

Evidence-based Mistakes – an example

Bromocriptine for suppression of lactation was reviewed by two groups. One group said the evidence of potential harm of the drug exceeded the benefits of lactation suppression, while another group concluded that the drug was effective without any serious adverse effects of concern. With greater use, the drug turned out to cause serious harm, including deaths. Absent or weak information on adverse effects and jumping to conclusions too soon cause evidence-based mistakes and "a promising treatment is generally just the larval stage of a disappointing one" (Bastian, 2004).

Generating evidence is a continuous and self-correcting process. Therefore, over a period of time, EBM should cause fewer errors in healthcare delivery than other options, especially the profit-driven medicine (ibid).

Misuse of Evidence by Insurers to Deny Therapy

Carr (2008) has stressed that powerful stakeholders in the healthcare enterprise were looking to EBM for answers about effectiveness, cost effectiveness, and appropriateness, beyond what EBM could reasonably provide. Data miners have been used to dig into the trial data and look for statistical evidence to support cost-cutting measures. This is an example of wrong application of evidence to support "pay for performance" and to restrict payment to the physicians and other care providers. Even as advances in pharmacogenomics have generated optimism about personalized medicine, the individualized care provided today in multidisciplinary pain

treatment programmes is under attack. "How often have pain clinicians been told by payers, while withholding of payment, that 'insufficient evidence to prove efficacy' is 'sufficient evidence to prove ineffectiveness'?" (ibid).

Industry-Led Distortions of EBM

McGoey (2009) has discussed how the withholding of "marketing unfriendly" clinical trial information by multi-national corporations (MNCs) and academic researchers distorts the evidence base, and could affect the reliability of clinical guidelines. Lack of effective regulatory controls has let the multinational drug industry continue doing this. A good case study is the failure of UK drug regulators to prosecute the manufacturer of Paroxetine HCl, a top-selling antidepressant, for withholding information on the potential risks of the drug from regulators.

Several MNC giants have been indicted for outright deception of the biomedical community by suppression of scientific truth, stalling or stopping the publication of negative study results, manipulating both trial designs and data to make the drug look more effective than it was, and using questionable tactics to enhance the drug's image and increase its sales. These practices were "highly unethical, harmful to science, wasteful of public resources, and potentially dangerous to the public's health" (Carmichael, 2009; Ross, 2009).

Some professionals in the pharmaceutical industry have turned "whistle-blowers" and have spoken out against the "sales and profits first" approach to drug development that has created problems for many. Unethical methods of promoting drugs (Rengen, 2009), including manipulating the medical professionals (Olsen, 2007) and direct-to-consumer advertising to create public demand to get expensive brands prescribed irrationally (Bellonzi, 2008), have been highlighted.

On the troublesome issue of commercial interests interfering with scientific truth, an editorial in *The Lancet* (2002) has concluded thus:

> "How tainted by commercial conflicts has medicine become? Heavily, and damagingly so, is the answer. A more important question arises: do those doctors who support this culture for the best of intentions – e.g., to undertake important research that would otherwise remain unfunded – have the courage to oppose practices that bring the whole of medicine into disrepute?"

Until the industrial, political, and legal barriers preventing full access to clinical trial data are addressed, the ideals of evidence-based practice will remain elusive (McGoey, 2009).

Evidence-Based Prescribing

The current enthusiasm for evidence-based prescribing is welcome and should lead to safer and more effective use of medicines. But it also poses some real problems for prescribers:

- Reliable evidence to guide everyday prescribing decisions at the point of prescription is hard to find;
- Evidence is often inconclusive, inconsistent with other reports, or irrelevant to clinical realities;
- Even when there is good evidence, different experts synthesize it to produce a variety of conclusions about optimal prescribing;
- When several are found, the prescriber has to decide which one of them is the most reliable, accurate, and representative of true evidence.

These shortcomings should not lessen prescribers' appetite for sound, evidence-based recommendations for rational prescribing (Maxwell, 2005).

Straus and Haynes (2009) have recently discussed the problems of practicing EBM and have suggested how it may be made more usable and effective. The sources of information for the practice of evidence-based healthcare should be reliable, relevant, and readable, in that order. They suggest a top down "5S" approach as a model for seeking evidence efficiently: from *systems*

(electronic database for EBM) to *summaries* (Dynamed, ClinicalEvidence etc), *synopses* (EBM journals), *syntheses* (Cochrane abstract), and *studies* (original articles).

Pressures on the Prescribers

Rational prescribing has been defined as prescribing that is effective, safe, appropriate, and affordable. Based on these criteria, much of the prescribing in general practice has been judged to be irrational.

A study by Bradley (1992) revealed the complexity of the decision making that precedes prescribing in general practice. "Prescribing discomfort" was found to be an everyday experience of the prescribers. This discomfort can occur for any of the prescribed drugs in any clinical condition. Many considerations, including medical, social, and logistic ones, influence the decision to prescribe in general practice. The final action taken depends on a complex interaction of these disparate influences and scientific evidence was only one among these influences.

Of the various factors that contributed to the difficulty in decision making, perceived 'want' versus real 'need' was found to be a common dilemma. Most of the doctors in the study needed training on how to avoid prescribing when it was not clinically indicated. They needed to acquire important "soft skills" of learning to say "no" and to make patients realize the difference between real need and perceived needs (ibid). There is a need for rational consumer education and empowerment, which may warrant prohibition of direct-to-consumer advertising of prescription drugs (http://www.nps.org.au/consumers).

Developing an evidence base that is appropriate to the resource settings could assist the prescriber in resource-poor settings to prescribe therapy rationally. A good example is the "DIAMOND study" – a primary-care-based randomized controlled trial on patients with dyspepsia – reported recently in the *Lancet* (van Marrewijk, et al., 2009).

What the Future Holds: Individualized Medicine

The future of medicine is currently being shaped by quantum leaps in bioinformatics, genomics and nano-medicine.

According to Hood (2009):

> "Driven by advances in genomics, bioinformatics, nano-medicine, and targeted disease prevention strategies, 'P-4 medicine' – predictive, personalized, preventive and participatory – is the future. Over the next two decades, medicine will change from its current reactive mode, in which doctors wait for people to get sick, to a mode that is far more preventive and rational. The new P-4 medicine will eventually lead to a universal democratization of health care, bringing to billions the fundamental right of health, unimaginable even a few years ago."

In the 21st century, individualized medicine may fully integrate the rational and the evidence-based approaches to therapy. On the other hand, commercialised P-4 medicine might be priced out of the reach of all but the rich!

Summing Up

Using EBM and RDU as two points of view, one could classify a prescription in one of the following four ways:

I. *It is evidence based as well as rational*: whenever possible, adhere to the win-win combination of rational therapy that is supported by strong evidence; an ideal solution.

II. *It is rational but is not evidence based*: rational approach should take precedence over EBM if in the opinion of the prescriber, the evidence is not appropriate for the individual patient concerned.

III. *It is evidence based but is irrational*: usually due to uncritical application of EBM, the so called 'cook book' approach. Clinical expertise is required to avoid such prescriptions.

IV. *It is irrational and not evidence based*: an avoidable option at most instances. An exception

may be if such an option is mindfully chosen to manage patient expectations – especially if a harmless and inexpensive intervention is used to enhance placebo or Hawthorne effects.

References

Bastian, H. (2004). Learning from evidence based mistakes. *British Medical Journal,* 329, p.1053. Available at: http://www.bmj.com/cgi/content/full/329/7473/1053

Bellonzi, V. (2008)."Big Pharma, Big Bucks (part-1)." Talk. 27 March 2008. YouTube. 11 November 2009. Available at: http://www.youtube.com/watch?v=c1Gxk6ohjHs

Bradley, C.P. (1992). Uncomfortable prescribing decisions: a critical incident study. *British Medical Journal,* 304, pp.294–96. Available at: http://www.bmj.com/cgi/content/abstract/304/6822/294

Carmichael, M. (2008). Pfizer's Headache. *Newsweek,* [Online] 8 Oct. Available at: http://www.newsweek.com/id/162906 [Accessed 11 November 2009].

Carr, D.B. (2008). When bad evidence happens to good treatments. *Regional Anesthesia and Pain Medicine,* 33, pp.229–40. Available at: www.ncbi.nlm.nih.gov/pubmed/18433675

Calabrese A, Coley K, DaPos S, Swanson D, Rau R. (2002). Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. Arch Intern Med.162:434-437 Available at: www.ncbi.nlm.nih.gov/pubmed/11863476

Donnell, R.W. (2006). Exploit Available Resources and Knowledge - in Centor RM, Marchetti P, Donnell RW, Poses RM. 2006. How Can Physicians Stay Current on Prescription Drugs? Medscape Med Students 8(2). Available at: http://www.medscape.com/viewarticle/543641_3 [Accessed 11November 2009].

Fanarow G, Yancy C, Haywood T. (2005). Adherence to heart failure quality-of-care indicators in US hospitals. Arch Intern Med.165:1469-1477. Available at: www.ncbi.nlm.nih.gov/pubmed/16009861

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Grimshaw, J.M. & Russell, I.T. (1993). Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *The Lancet*, 342, pp.1317–22. Available at: www.ncbi.nlm.nih.gov/pubmed/7901634

Hood, L. (2009). A doctor's vision of the future of medicine. *Newsweek,* [Online] 13 July. Available at: http://www.newsweek.com/id/204227 [Accessed 11-11-2009].

Maxwell, S.R.J. (2005). Evidence based prescribing (Editorial). *British Medical Journal,* 331, p.247. Available at: www.ncbi.nlm.nih.gov/pubmed/16051992

McGoey, L. (2009). Sequestered evidence and the distortion of clinical practice guidelines. *Perspectives in Biology and Medicine,* Spring, 52(2), pp.203–17. Available at: www.ncbi.nlm.nih.gov/pubmed/19395820

Moores, K.G. (1997). Current clinical issues: search strategies. *World of Drug Information,* [Online] March, 8 (1). Available at: http://www.uiowa.edu/~idis/wodmar97.htm [Accessed 18 December 2009].

Olsen, G. (2009)."Manipulating Doctors". Talk. 6 July 2007.YouTube. 11 November 2009. Available at: http://www.youtube.com/watch?v=kOW8LNU2hFE

Poses, R.M. (2006). Embrace evidence-based medicine. *Medscape Med Students,* [Online] 8(2). Available at: http://www.medscape.com/viewarticle/543641
[Accessed 11 November 2009].

Rengen, J.V. (2009). "Big Pharma Whistleblower speaks out at the AZK in Germany". Talk in 4 parts. 9 July 2009. YouTube. 11 November 2009.
Available at: http://www.youtube.com/watch?v=2NuAQ-x2Ijc

Ross, J.S. (2009). Pooled analysis of rofecoxib placebo-controlled clinical trial data. *Archives of Internal Medicine,* pp.1976–84. Available at: www.ncbi.nlm.nih.gov/pubmed/19933959

Sackett, D.L., et al. (1996). Evidence-based medicine: What it is and what it isn't. *British Medical Journal,* 312, pp.71–72. Available at:
http://www.bmj.com/cgi/content/full/312/7023/71

Straus, S., & Haynes, R.B. (2009). Managing evidence-based knowledge: the need for reliable, relevant and readable resources. *Canadian Medical Association Journal,* 180, pp.942–45. Available at: www.ncbi.nlm.nih.gov/pubmed/19398741

The Lancet Editorial (2002). Just how tainted has medicine become? *The Lancet,* 359, p.1167. Available at: www.ncbi.nlm.nih.gov/pubmed/11955529

To cite this article: Sethuraman., K.R. (2012). The Role of Evidence-Based Medicine in Rational Drug Use. The Politics of Medicines (e-Encyclopaedia). Available at: https://haiweb.org/encyclopaedia/evidence-based-medicine/

van Marrewijk, C.J., et al. (2009). Effect and cost-effectiveness of step-up versus step-down treatment with antacids, H2-receptor antagonists, and proton pump inhibitors in patients with new onset dyspepsia (DIAMOND study): a primary-care-based randomised controlled trial. *The Lancet,* 373, pp.215–25. Available at: www.ncbi.nlm.nih.gov/pubmed/19150702

Key references on EBM

Australian Therapeutic Guidelines: http://www.tg.com.au

BMJ Evidence Centre: http://group.bmj.com/products/evidence-centre

Cochrane Library: http://www.cochrane.org.au/libraryguide/

EBM sources: http://www.ebmsources.fmed.ulaval.ca/

NHS Evidence: http://www.evidence.nhs.uk/

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Author's Biography (in brief)

Professor K. R. Sethuraman, MD is currently the dean and professor of Medicine of the Faculty of Medicine, and the deputy Vice-chancellor of Academic Affairs of the AIMST University in Malaysia (www.aimst.edu.my). Earlier, he was in academics at JIPMER, India (www.jipmer.edu). He and his colleagues at JIPMER founded the "Society of Educators for Quality Update for Indian Physicians" in 1991, which is an active partner of ERDU (Educators of Rational Drug Usage) launched by HAI-SEAROAP. They have brought out trainers' resources: a video on drug promotion ("Push, Promote or Educate?") and a manual ("Beyond Rational Therapy").

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