Ann Ist Super Sanità 2011 | Vol. 47, No. 1: 26-30
DOI: 10.4415/ANN_11_01_07

Integrating clinical research into clinical decision making

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Summary. Evidence-based medicine has placed a general priority on knowledge gained from clinical research for clinical decision making. However, knowledge derived from empiric, population-based research, while valued for its ability to limit bias, is not directly applicable to the care of individual patients. The gap between clinical research and individual patient care centers on the fact that empiric research is not generally designed to answer questions of direct relevance to individual patients. Clinicians must utilize other forms of medical knowledge, including pathophysiologic rationale and clinical experience, in order to arrive at the best medical decision for a particular patient. In addition, clinicians must also elucidate and account for the goals and values of individual patients as well as barriers and facilitators of care inherent in the system in which they practice. Evidence-based guidelines and protocols, then, can never be prescriptive. Clinicians must continue to rely on clinical judgment, negotiating potentially conflicting warrants for action, in an effort to arrive at the best decision for a particular patient.

Key words: evidence-based medicine, clinical decision making, medical epistemology.

Riassunto *(Integrare la ricerca nella decisione clinica)*. La medicina basata sull'evidenza (*evidence-based medicine,* EBM) pone la priorità sulla conoscenza acquisita tramite le ricerche finalizzate a decisioni cliniche. Tuttavia, la conoscenza derivante da ricerche empiriche, basate sulla popolazione, sebbene sia di riconosciuta capacità nel limitare le distorsioni, non è direttamente applicabile alla cura individuale dei pazienti. Il divario tra la ricerca clinica e la cura del singolo paziente dipende dal fatto che la ricerca empirica non è in genere progettata con l'intento di rispondere a domande di rilevanza diretta per il singolo paziente. I clinici si devono avvalere di altre forme di conoscenza medica, che includano un razionale fisiopatologico e l'esperienza clinica, al fine di giungere alla miglior decisione clinica per un dato paziente. Inoltre, i clinici devono anche spiegare e rendere conto degli obiettivi e dei valori dei singoli pazienti, come pure degli ostacoli e degli elementi positivi della cura relativi al sistema nel quale operano. Quindi, le linee-guida e i protocolli EBM non dovrebbero mai essere prescrittivi. I clinici devono continuare a basarsi sul giudizio clinico, bilanciando interventi potenzialmente in conflitto, con l'obiettivo di giungere alla decisione migliore per un determinato paziente.

Parole chiave: medicina basata sull'evidenza, decisioni cliniche, epistemologia medica.

INTRODUCTION

Evidence-based medicine (EBM), which focuses on the development, acquisition, critical appraisal and incorporation of evidence derived from clinical research into clinical practice, promises a more uniform and scientific foundation for clinical practice [1]. Yet there is a gap between the kind of knowledge generated by clinical research studies and the kind of knowledge necessary to make the best decision for individual patients [2]. And while EBM has focused on aiding clinicians in acquiring and appraising the result of clinical research, little effort has been spent on aiding clinicians in actually integrating such knowledge with other important considerations in clinical practice [3]. As a result of this limited emphasis, EBM has failed to provide an adequate account of optimal medical practice.

THE GAP BETWEEN CLINICAL RESEARCH AND CLINICAL PRACTICE

The intrinsic gap between clinical research and clinical practice can be understood in two ways [2]. First, the type of knowledge we gain from well-designed clinical trials and systematic reviews is not the kind of knowledge clinicians need when facing a particular clinical problem. Clinical research methods, and particularly the randomized, controlled trial (RCT), provide powerful tools for determining the efficacy of an intervention by eliminating the background noise created by individual variability in the way disease presents and healing occurs. This provides a type of empirical knowledge that tells us something about how an intervention affects an "average" patient or what would likely re-

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sult from the application of an intervention across a population [4]. The question faced by clinicians, however, is not whether a therapy works on average (although this might be an appropriate question for the Agenzia Italiana del Farmaco – AIFA – or public health officials), but whether it will work in the patient-at-hand. At best, clinical research can provide for us some probabilistic information, but it can never directly answer a specific clinical question. The type of knowledge gained from clinical research is informative, but insufficient for clinical decision making.

The gap between clinical research and clinical practice is an ethical gap as well [2]. A traditional distinction exists in moral philosophy between statements of fact and statements of value and general consensus exists that statements of value cannot follow directly from statements of fact [5]. That is, value judgments need to be included in any argument from facts if we hope to arrive at a conclusion regarding what ought to be done in a particular situation. In medicine, this means that knowledge derived from clinical research is never ethically prescriptive; clinical research cannot tell us what we ought to do. To make the jump from research to practice we need to consider values, those of the patient, of the profession, and/or of society.

Clinical research alone does not provide us with the type of knowledge we need to make decisions about the care of individuals nor is it applicable without an understanding of social, professional and personal goals, values and preferences. The clinician requires more tools than evidence-based medicine has thus far provided in order to bridge this gap.

BRIDGING THE GAP BETWEEN CLINICAL RESEARCH RESULTS AND PRACTICE

As noted above, the gap between clinical research and clinical practice represents both a knowledge gap and a values gap. EBM clearly now recognizes the values gap and cautions all practitioners that patient preferences and values must be incorporated into clinical decision making [6]. A branch of EBM now strives to find a more explicit and objective way to incorporate values into decision making through the use of standardized values assessment tools. The ultimate success of this "patient utilities" movement remains in doubt, but a discussion of the advantages and disadvantages of this approach is beyond the scope of this work [7].

Bridging the knowledge gap has garnered less attention, as this gap is not fully acknowledged by many in EBM [8]. The part of this gap due to the relative paucity of empirical evidence to help guide medical decisions is often noted by proponents of EBM, virtually always followed by a call for more funding to perform clinical research. Yet, regardless of the quality and quantity of empirical evidence, this gap will remain and clinicians will need sound clinical judgment to help them overcome it [9].

Several approaches to overcoming this knowledge gap exist, and these may be pursued simultaneously. One approach would be to fully reject the tenets of EBM and to develop a more inclusive model for clinical practice, a medicine of the whole person. Another is to attempt to make research truly personal, by focusing on genomic information particular to individuals [10]. The promise of such a strategy is advanced in this issue by Dr. Dhavendra Kumar [11]. But in the short term at least, and likely for the many years to come, clinicians will need to find a way to incorporate the imperfect knowledge generated by clinical research with other forms of medical knowledge to arrive at the best choice for an individual patient. This requires understanding the different kinds of medical knowledge that ought to be brought to bear in clinical decisions and, furthermore, the strengths and weaknesses of each.

Five topics constitute the universe of potential warrants for clinical decision making [9]. These topics are summarized in *Table 1*. The first three (results from clinical research, clinical experience and pathophysiologic reasoning) represent distinct forms of medical knowledge, differing in kind from one another. Each has particular strengths and weaknesses when applied to clinical decisions. Since they differ in kind, they cannot be ranked or placed in a hierarchy; no form of medical knowledge always takes precedence over the others. Examining and weighing the medical knowledge applicable to a particular case represents sound clinical judgment.

Table 1 | *The five topics of clinical decision making*

Topic	Explanation
Results of clinical research	Empirical results published in the medical literature
Clinical experience	Derived from personal clinical experience or the clinical experience of others (i.e. expert opinion)
Pathophysiologic rationale	Based on underlying theories of physiology, disease and healing
Patient values and preferences	Derived from personal interaction with individual patients
System features	Including resource availability, societal, religious and professional values, legal and cultural concerns

Modified from: Tonelli MR. Integrating evidence into clinical practice: an alternative to evidence-based medicine approaches. J Eval Clin Prac 2006;12(3):248-56 [3].

STRENGTHS AND WEAKNESSES OF KINDS OF MEDICAL KNOWLEDGE FOR CLINICAL PRACTICE

Empirical research becomes knowable to the practicing physician through published reports. Teaching how to access, interpret, and critically appraise the published reports of empirical studies has become a major focus of Western medical education [12]. The value of relying on this kind of medical knowledge is well catalogued by proponents of EBM. The major limitations of empirical research relates to the fact that it cannot be directly applied to any particular patient [2, 4]. This means that the results of clinical research cannot be deductively applied to individual patients; clinical research is never prescriptive. Additionally, clinical research is fixed in time and place, not necessarily generalizable to other places and later times. Nor is empirical research infallible or always trustworthy [13].

Clinical experience encompasses the knowledge gleaned from the direct care of patients. Direct experiential knowledge differs in meaningful ways from processed knowledge, such as published reports of study results [14]. The practicing physician may rely on personal experience or attempt to learn from the personal experience of others. With experiential knowledge, more is generally considered better than less. Hence, expert opinion, when based on extensive experience with large numbers of patients with a particular disease, may be viewed as the highest form of experiential evidence [15]. Experience provides a tool to assess whether differences in individual patients are compelling enough to alter diagnostic or treatment strategies by providing a rich set of cases to which a new patient can be compared. The major problem with experiential knowledge is that it is prone to multiple kinds of cognitive bias [16], with potentially false conclusions about causality or treatment effect being drawn. In addition, clinical practice tends to be static, meaning clinicians may be slow to adopt more promising strategies given that experience alone has not provided a motivation to change one's pattern of practice.

Pathophysiologic reasoning follows from the general Western understanding of illness as a perturbation of the physical self. Understanding basic biologic and physiologic principles allows physicians to both relate presenting features to a diagnosis and to anticipate and measure response to therapy, again allowing for individualization of therapeutic decisions. Assessing physiologic response allows for early recognition of therapeutic effect or failure. The major limitation of reasoning from scientific principles centers on the uncertain relationship between physiologic measures and meaningful outcomes, such as mortality and quality of life. Furthermore, reasoning from physiologic and biologic principles can only be as good as our understanding of the basic science allows.

PRACTICAL CLINICAL REASONING

Sound clinical judgment requires that reasoning start with the individual patient, eventually incorporating relevant knowledge from all the topic areas. Clinical research, when well done, may provide clinicians with a recommended action for a "typical" or "average" case. The clinician must decide whether the patient-at-hand resembles the average patient provided by the clinical research closely enough to warrant incorporating the conclusions of that research into that patient's care. Since the patient will almost always differ in some way from the average study subject, the clinician must decide whether those differences are important enough to mean the conclusions drawn from the study are not relevant to the current decision. How closely the patient-at-hand resembles the "average" patient in a study will determine how much weight to give the study results. At times, clinicians must ask whether the patient-at-hand more closely resembles those enrolled in one study or in another that yielded a different result. But clinicians must also compare the patient to real cases from the clinician's personal experience and perhaps patients, individual or in aggregate, from the experience of expert colleagues. Pathophysiology plays into this process, aiding the clinician in weighing whether differences in patients presentation are likely to be relevant to diagnostic or therapeutic choices. Such differences must also be considered to see if they represent important enough distinctions to reject the provisional conclusions about the present case. Eventually, patient goals and values will have to be considered in order to arrive at a presumptive conclusion regarding the best course of action.

Clinical judgment, then, represents a provisional conclusion on the part of clinicians, a conclusion based upon consideration of multiple pieces of medical knowledge, not simply the results of clinical research. Such a process is a far cry from the deductive approach advocated in EBM, an approach that is based upon a false assumption that results of clinical research are directly applicable to individual patients. The case-based reasoning described above is patient-centered and leaves room for variation in clinical practice. Clinical research alone can never provide a demonstrably "best" course of action in any treatment decision. Rather, clinicians will need to continue to consider experience and pathophysiology in every patient encounter.

CLINICAL JUDGMENT JUDGED

The general stance of EBM has been that when sound clinical research exists upon which evidence-based guidelines can be derived, clinical judgment that allows for incorporation of clinical experience or pathophysiologic reasoning cannot be trusted. Recently, however, empiric evidence to the contrary has been published. Persell and colleagues, working in a closed health care delivery system with electron-

ic health care records in the United States, prompted physicians to make explicit their reasoning for deviating from evidence-based practice guidelines for the management of diabetes, heart failure, and prevention and screening [17]. Deviations from guidelines were relatively common. Peer review was performed for each example of a deviation from a practice guideline and only 3% of all such exceptions were deemed to be inappropriate. It appears that clinicians recognize that the results of clinical research and generalizations from that research to practice guidelines do not always apply to the more complex patients they deal with, those with multiple co-morbidities and varied manifestations of illness. Physicians are left to perform a risk/benefit calculation based on factors other than clinical research (Persell SD, personal communication). Currently, physicians appear to have the skills necessary to perform this task well. It is possible, however, that over-emphasizing the skill set embraced by EBM will result in the next generation of clinicians being unable or unwilling to perform the more complex task of clinical judgment described above.

COMPELLING CLINICAL RESEARCH

The intrinsic epistemic gap between the results of clinical research and the practice of clinical medicine has been unnecessarily widened by the focus of clinical researchers, under the guidance of methodologists, on aspects of study design that limit bias and increase power, but often result in research that is not compelling to clinicians. That is, the focus has far too often been on the "strength of evidence", as determined by study design, rather than designing a study to answer questions most important to clinicians. Statistical robustness is given priority over clinical relevance.

For a study to be compelling to clinicians, it must be applicable to the kinds of patients a physician treats, not a narrowly defined sub-group. The results will be more compelling if they are consistent with prior understanding and have biologic plausibility. The outcomes measured should be of high value to patients and clinicians alike, preferably with an effect size large enough that physicians can reasonably expect that changing their practice will result in a noticeable change in outcomes. Clinicians care about cost and safety. They are more likely to adopt an approach that is easily implemented and is likely to show results in relatively short order. Most of these features have nothing to do with validity or robustness of the trial, so valued by methodologists. But even the most robust results are easily ignored by clinicians if they are not compelling in some other way, if they do not seem relevant to one's own practice. The EBM movement could become much more valuable to clinicians if they were to focus on designing studies likely to be compelling rather than those which will stand a statistical acid test.

CONCLUSIONS

A careful analysis of the kind of knowledge generated by clinical research reveals that attempts to view such knowledge as prescriptive in individual clinical decision making is in error. The five topics relevant to any particular clinical decision are: 1) results of empirical research; 2) experiential knowledge; 3) pathophysiologic understanding; 4) patient goals and values, and 5) system features. The skilled clinician, then, must weigh these potentially conflicting warrants for action when dealing with the patient-at-hand, employing both practical and theoretical reasoning and comparing the patient to paradigmatic cases from both the literature and experience, before coming to a presumptive conclusion regarding the appropriate course of action. There is no hierarchy of medical knowledge or medical evidence for clinical practice. In particular cases, pathophysiologic reasoning or clinical experience may override the results of clinical research. This understanding of clinical medicine has important implications for medical education as well as the provision of healthcare. Clinicians must be trained and allowed to deviate from clinical practice guidelines and protocols. The personal and prudential nature of clinical decision making means that clinicians may reasonably differ in assessments, conclusions and recommendations regarding the care of individual patients. The optimal practice of clinical medicine, though dependent upon the knowledge of the results of clinical research, will still require physicians with the ability to go beyond the simple application of empirical evidence to particular cases, utilizing all of their knowledge in an attempt to benefit individual patients.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Submitted on invitation.
Accepted on 20 September 2010.

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