CHAPTER 3

Evidence-Based Medicine

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KEY CONCEPTS

1. The best current evidence integrated into clinical expertise ensures optimal care for patients.
2. The four steps in the process of applying evidence-based medicine (EBM) in practice are (a) formulate a clear question from a patient's problem, (b) identify relevant information, (c) critically appraise available evidence, and (d) implement the findings in clinical practice.
3. The decision as to whether to implement the results of a specific study, conclusions of a review article, or another piece of evidence in clinical practice depends on the quality (i.e., internal validity) of the evidence, its clinical importance, whether benefits outweigh risks and costs, and its relevance in the clinical setting and patient's circumstances.
4. EBM strategies can be applied to help in keeping current.
5. EBM is realistic.

In the information age, clinicians are presented with a daunting number of diseases and possible treatments to consider as they care for patients each day. As knowledge increases and as the technology for accessing information becomes widely available, healthcare professionals are expected to stay current in their fields of expertise and to remain competent throughout their careers. In addition, the number of information sources for the typical practitioner has ballooned, and clinicians must sort out information from many sources: college courses and continuing education (including seminars and journals), pharmaceutical representatives, and colleagues, as well as guidelines from committees of healthcare facilities, governmental agencies, and expert committees and organizations.

1 How does the healthcare professional find valid information from such a cacophony? Increasingly, clinicians are turning to the principles of evidence-based medicine (EBM) to identify the best course of action for each patient. EBM strategies help healthcare professionals to ferret out these gold nuggets, enabling them to integrate the best current evidence into their pharmacotherapeutic decision making. These strategies can help physicians, pharmacists, and other healthcare professionals to distinguish reliably beneficial pharmacotherapies from those that are ineffective or harmful. Also, EBM approaches can be applied to keep up-to-date and to make an overwhelming task seem more manageable.

This chapter describes the principles of EBM, offers guidance for finding EBM sources on the World Wide Web, provides a model for applying EBM in patient care, and explains how EBM strategies can help a practitioner stay current.

WHAT IS EVIDENCE-BASED MEDICINE?

EBM is an approach to medical practice that uses the results of patient care research and other available objective evidence as a component of clinical decision making. Similarly, evidence-based pharmacotherapy, defined by Etminan et al.,[1] is an approach to decision making whereby clinicians appraise the scientific evidence and its strength in support of their therapeutic decisions.

Although few would argue against the necessity for basing clinical decisions on the best possible evidence available, considerable controversy actually surrounds the practice of EBM. Critics note that not all questions relevant to the care of a patient are of a scientific nature and that EBM favors a "cookbook" approach. In fact, EBM integrates knowledge from research with other factors affecting clinical decision making. EBM does not replace clinical judgment. Rather, it informs clinical judgment with the current best evidence. The expertise and experience of the clinician who understands the disease are crucial in determining whether the external evidence applies to the patient and whether it should be integrated in the therapeutic plan. Also, nonmedical factors affect decision making, such as the patient's preferences and readiness and the healthcare delivery system's characteristics.

Other critics state that EBM considers randomized controlled trials (RCTs) as the only evidence to be used in clinical decision making. Actually, EBM seeks the best existing evidence, from basic science to clinical research, with which to inform clinical decision. For example, a decision about the accuracy of a diagnostic test is best informed by evidence from a cross-sectional study, not a RCT. A cohort study, not a RCT, best answers a question about prognosis. However, in selecting a treatment, the RCT is the best study design to provide the most accurate estimate of treatment efficacy and safety.

EBM opponents note that RCTs usually are conducted in idealized environments or situations that are not sufficiently similar to the conditions of the "real world." In addition, errors can be made when results of an RCT of one drug are extrapolated to all members of that class of drugs.[2,3]

Regardless of one's view, RCTs have confirmed the value of many therapeutic options today and have disproved or clarified the usefulness of others. For example, in 1970, observational studies had indicated a possible association between the occurrence of prema-

ture ventricular contractions (PVCs) in patients after myocardial infarction (MI) and sudden death. As a result, the eighth edition of *Harrison's Principles of Internal Medicine* recommended the use of antiarrhythmic agents to eradicate post-MI PVCs and thereby minimize the risk of sudden death. However, an RCT tested the antiarrhythmic therapy in patients with frequent PVCs, and it showed that class I antiarrhythmic agents increased rather than decreased the risk of sudden death.[4,5] Today, guidelines discourage the use of antiarrhythmic agents to suppress PVCs in post-MI patients.[6]

More recently, the 1996 guidelines for the management of patients with acute MI concluded that observational studies "indicate that estrogen therapy does reduce mortality in women with moderate and severe coronary disease."[7] Subsequently, an RCT found no reduction in overall risk for nonfatal MI or coronary death with estrogen therapy. Rather, significantly more coronary events occurred during the first year of the trial among women receiving estrogen therapy compared with women taking placebo.[8] These results prompted revision of the guidelines to conclude: "On the basis of the finding of no overall cardiovascular benefit and a pattern of early increase in risk of coronary events, starting estrogen plus progestin is not recommended for the purpose of secondary prevention of coronary disease."[6]

In both these examples, conventional wisdom was wrong. Results from observational studies proved incorrect. Only through careful assessment using RCT methodology was the true estimate of the efficacy and safety of the therapeutic options discovered.

CLINICAL CONTROVERSY

In many ways, EBM is controversial, with some people believing that it prevents the application of common sense and experience-based reasoning to clinical care. Some joke that a clinician called an EBM center and asked whether parachutes are effective when jumping from a plane. "We do not know," came the response. "There are no randomized controlled trials comparing jumping from a plane with and without one!"

EVIDENCE-BASED MEDICINE ON THE WORLD WIDE WEB

Several comprehensive EBM sites exist on the World Wide Web, providing additional information and resources relevant to EBM. These sites include information on the history and development of EBM, glossaries of EBM terms, tutorials, training programs, software, links to EBM organizations and practice centers, guides to searching the medical literature, and results of evidence-based studies. For an excellent list of EBM links, access "Netting the Evidence: A ScHARR Introduction to Evidence Based Practice" (*http://www.shef.ac.uk/~scharr/ir/netting/*).

INCORPORATING EVIDENCE-BASED MEDICINE INTO PHARMACOTHERAPEUTIC DECISION MAKING

2 The practice of EBM is to recognize an information need while caring for a patient, identify the best existing evidence to help resolve the problem, consider the evidence in light of the actual circumstances, and integrate the evidence into a medical plan. In this section, the four steps involved in applying the EBM process to a pharmacotherapeutic decision are described[9]:

1. Recognize information needs and convert them into answerable questions.
2. Conduct efficient searches for the best evidence with which to answer these questions.
3. Critically appraise the evidence for its validity and usefulness.
4. Apply the results to patient situations to best assist clinical decision making.

BUILDING A FOCUSED QUESTION

Clinicians constantly balance the benefits and risks of various therapeutic choices. The questions they face are patient-specific:

- Should clopidogrel be prescribed to this 65-year-old man with unstable angina?
- Should hormone-replacement therapy be prescribed for this postmenopausal woman?
- Is sildenafil safe in this patient with type 2 diabetes?

When searching for the best evidence to answer such questions, the questions must be rephrased with more precision and specificity. A well-formulated question includes the following elements: the patient or problem being addressed, the intervention being considered, the comparison intervention, and the outcome(s) of interest.[10] Using these four elements, the preceding questions can be reframed as follows:

- Would clopidogrel in addition to aspirin (*intervention*) prevent death or coronary events (*clinically relevant outcome*) in this patient with unstable angina (*patient with a problem*) who is currently on aspirin alone (*comparison intervention*)?
- Should we begin hormone-replacement therapy (*intervention compared with no intervention*) to prevent cardiovascular events (*outcome*) in this asymptomatic postmenopausal woman with a family history of coronary artery disease (*patient*)?
- If sildenafil is begun (*intervention*), what is the risk of myocardial ischemia (*outcome*) in this asymptomatic patient with known coronary artery disease (CAD) and newly diagnosed with type 2 diabetes (*patient*)?

The acronym *PICO* can be helpful to remember the elements of a well-balanced question[11]:

P = patient
I = intervention
C = comparison
O = outcome

Focusing the question clarifies the target of the literature search and permits use of the appropriate guides for assessing external validity, that is, the applicability of the evidence found in the study to appropriate parts of the "real world."

CONDUCTING AN EFFICIENT SEARCH

Healthcare professionals have four options as they try to identify the best evidence available to answer a well-framed question:

1. Ask a colleague for his or her expert opinion.
2. Review practice guidelines (evidence-based or expert opinion-based) or a textbook for appropriate disease management.
3. Consult electronic databases of systematic reviews and/or meta-analyses.
4. Conduct a literature search using an electronic database such as MEDLINE.

Each of these options has advantages and disadvantages, as described below.

Option 1

Asking an expert or colleague may provide a quick and easy answer to a clinical question. Exercise caution, however. These sources have

TABLE 3-1 North American Sources of Evidence-Based Clinical Practice Guidelines

National Guideline Clearinghouse (NGC) (*www.guideline.gov*)	
NGC is a collaboration of U.S. Department of Health and Human Services and the Agency for Healthcare Research and Quality (AHRQ), in partnership with the American Medical Association (AMA) and the American Association of Health Plans (AAHP). NGC provides access to full text guidelines (when available) produced by a number of different professional medical associations and healthcare organizations. Each guideline is critically appraised using a standard instrument. The site permits side-by-side comparison of several guidelines.	• 1,823 guideline summaries • Weekly e-mail alerts • Advanced search queries based on guideline attributes, side by side comparison of guidelines • Annotated bibliography of resources relevant to guideline methodology • Palm-based PDA downloads
National Library of Medicine's Health Services/Technology Assessment Text (*hstat.nlm.nih.gov/*)	
This World Wide Web resource is a collection of AHRQ Supported Guidelines, AHRQ Technology Assessments and Reviews, ATIS (HIV/AIDS Technical Information), NIH Warren G. Magnuson Clinical Research Studies, NIH Consensus Development Program, Public Health Service (PHS) Guide to Clinical Preventive Services and the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Prevention Enhancement and Treatment Improvement Protocols.	• 644 full-text guidelines • Metasearch capabilities to PubMed, Centers for Disease Control and Prevention (CDC) Prevention Guidelines Database, and National Guideline Clearinghouse • Access to quick-reference guides for clinicians and to consumer brochures
Primary Care Clinical Practice Guidelines (*http://medicine.ucsf.edu/resources/guidelines*)	
This web resource offers a listing of online guidelines.	• Searchable by clinical content and organization
CDC Prevention Guidelines Database Home Page (*http://www.phppo.cdc.gov/cdcrecommends*)	
The site is a comprehensive collection of all the official guidelines and recommendations published by the CDC about prevention of diseases, injuries, and disabilities.	• More than 500 prevention guidelines/documents • Searchable • Sort by date, by topic, or alphabetically
Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) (*http://www.cancercare.on.ca*)	
This web page includes published and unpublished guidelines related to cancer care. These guidelines are created by the CCOPGI and are available full text.	• More than 100 guidelines • When information is scarce, evidence summaries are created to review the best evidence available
Agency for Healthcare Research and Quality's Evidence-Based Practice Centers (AHRQ EPCs) (*http://www.ahcpr.gov/clinic/epcix.htm*)	
AHRQ has established 12 Evidence-Based Practice Centers to analyze and synthesize the scientific literature and develop evidence reports and technology assessments on clinical topics.	• More than 160 evidence reports • Full text available

become less reliable as the volume and complexity of medical information have grown exponentially. Colleagues may be out of date or biased by their own experiences.

Option 2

Online practice guidelines or current textbooks with evidence links are useful if the question relates to a common or well-established issue (e.g., *UpToDate, Harrison's Online,* and *Scientific American Medicine Online, Clinical Evidence Concise* electronic textbooks). As their names suggest, evidence-based clinical guidelines are guided by objective data and should be preferred over expert opinion-based guidelines that refer loosely to evidence to support their opinions. Expert opinion guidelines vary in their scientific validity and reproducibility.[12]

One website—the National Guideline Clearinghouse on the Web (*http://www.guideline.gov*)—provides links to many evidence-based clinical practice guidelines. For each guideline, this comprehensive database offers a short summary of the key attributes, including the bibliographic sources, guideline developers and endorsers, status of the guidelines, and major recommendations. In addition, the site provides the ability to generate side-by-side comparisons for any combination of two or more guidelines. Table 3–1 presents an annotated list of additional resources to find and access evidence-based clinical practice guidelines.

Option 3

Consulting electronic databases of systematic reviews and meta-analyses is attractive because of the limited amount of time healthcare professionals have to research and review the literature before they answer clinical questions or reach patient care decisions. Busy healthcare professionals prefer summaries of information. Traditional narrative reviews are useful for broad overviews of particular therapies or diseases or for reports on the latest advances in a particular area where research may be limited.[13] However, information from narrative reviews is often gathered ad hoc, and the author's biases may enter into the process of gathering, analyzing, and reporting information.

In contrast, systematic reviews employ a comprehensive, reproducible data search and selection process to summarize all the best evidence. They follow a rigorous process to appraise and analyze the information, quantitatively (through the meta-analysis technique) or qualitatively, to best answer a defined clinical question. Systematic reviews are a useful means of assessing whether findings from multiple individual studies are consistent and can be generalized.[14]

The Cochrane Library represents one of the most comprehensive sources of systematic reviews summarizing the evidence about healthcare. More than 3,000 Cochrane reviews are currently available, and another 1,658 reviews were in progress when this chapter was finalized in January 2007. Because new reviews are added quarterly, eventually all areas of healthcare will be covered. The Cochrane Library includes the Database of Abstracts of Reviews of Effectiveness, which contains about 6,000 structured abstracts of good quality, published reviews about the effectiveness of health interventions. Table 3–2 lists accessible sources of systematic reviews and provides a search strategy developed by librarians at McMaster University to locate systematic reviews and meta-analyses on MEDLINE efficiently.[15]

Option 4

Consider conducting a literature search on an electronic database such as MEDLINE if the question relates to new developments in therapeutic options. In this case, healthcare professionals must consult primary literature. Dozens of electronic databases exist as primary sources of original research reports.

TABLE 3-2 Selected Resources for Systematic Reviews

Resources	Advantages	Disadvantages
Best Evidence Electronic version of both American College of Physicians (ACP) Journal Club and Evidence-Based Medicine (*http://hiru.mcmaster.ca/acpjc/acpod.htm*); available on CD-ROM	• All review articles are systematic reviews • Updated every 6 months • Short title includes meta-analysis or review to facilitate identification	• Includes systematic reviews only from the journals scanned by ACP Journal Club and Evidence-Based Medicine
MEDLINE Systematic review search strategy: (meta-analy$ or metanal$ or metaanal$).tw. or Meta-Analysis/or meta-analysis (pt) or (quantitativ$ review$ or quantitativ$ overview$).tw. or (systematic$ review$ or systematic$ overview$).tw. or (methodologic$ review$ or methodologic$ overview$).tw. or medline.tw. or pooled.tw.) and eng.lg. and human/) not (letter or editorial or comment).pt	• Covers more than 4,000 journals • Contains 11 million citations	• One-tenth of the citations are indexed as review articles. Even fewer are indexed as systematic reviews. • Requires search strategy to identify meta-analysis or systematic reviews
Cochrane Library Electronic library of high-quality reviews (*http://www.cochrane.org*); available on CD-ROM.	• Most comprehensive collection of systematic reviews • Updated every 3 months • Abstracts of Cochrane Reviews are available free on the Internet at *http://www.cochrane.org*	• Limited access; not all libraries subscribe to the Cochrane Library
United Kingdom National Health Services Centre for Reviews and Dissemination (*http://agatha.york.ac.uk/welcome.htm*) Includes the Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic evaluation database, and the Health Technology Assessment (HTA) database	• The DARE Web version, which is updated monthly, is more current than the Cochrane Library version; contains more than 30,000 abstracts; e-mail alerts	• Significant delay between original publication and entry into the CRD databases
Effective Health Care Bulletins (*http://www.york.ac.uk/inst/crd/ehcb.htm*)	• Reports of systematic reviews produced by NHS Centre for Reviews and Dissemination	• Limited number of reviews
National Institute for Clinical Excellence Part of the UK National Health Service (NHS). Provides guidelines and technology assessments to health care practitioners (*http://nice.org.uk*)	• Follows Cochrane methodology to develop technology assessments; more than 600 appraisals	• Limited number of guidelines and assessments available

MEDLINE and PubMed, both produced by the National Library of Medicine (NLM), are the largest and best known bibliographic databases of biomedical journal literature. PubMed's in-process records provide basic citation information and abstracts *before* the citations are indexed with NLM's Medical Subject Headings (MeSH) Terms and added to MEDLINE. To optimize the efficiency of a clinical search, PubMed offers specialized searches using methodologic filters. These filters, based on work by Haynes et al.,[15] are validated search strategies to identify clinically relevant studies that answer questions about etiology, prognosis, diagnosis, or therapy of a disease.

To facilitate the searches of multiple Internet sources, metasearching is useful. Metasearch tools launch a single query across a set of web-based health sites. One query returns a merged and often ranked list of hits, allowing the user to search several databases at once. Table 3–3 describes the specifics of new metasearch engines available to search for Internet-based health information.

Once the evidence is gathered, the clinician needs to determine whether the identified guideline, review article, or study report will help to answer the clinical problem. This is accomplished by considering the validity and by judging the clinical relevance (usefulness) of the information.[16]

ASSESSING VALIDITY

3 The *external validity* refers to applicability and generalization and is outlined in Applying the Results below. The remainder of this section focuses on critically appraising the quality—that is, the *internal validity*—of individual trials. The internal validity is determined by how well the trial ensures that the known and unknown risk factors are equally distributed between the treatment and control groups. To ensure validity, the conduct of the trial should minimize systematic bias and random error as much as possible to provide results that are as accurate and close to the truth as possible. Four sources of bias are possible in trials of healthcare interventions: selection bias, performance bias, attrition bias, and detection bias. Bias can result in an overestimation or underestimation of the effectiveness of a drug therapy and mislead the reader. Although it is beyond the scope of this chapter to present extensive details about critical appraisal (refer to Table 3–4 for additional resources on critical appraisal), here are three questions that must be answered in assessing the internal validity of an RCT:

- *Was the subject's treatment allocation randomized?* To minimize selection bias, all participants should have an equal chance to be allocated to the treatment or control group. Randomization is the best method to create groups of similar known and unknown confounders. If important risk factors known to affect prognosis (such as disease severity or presence of comorbidities) are unevenly distributed between groups, then selection bias could falsely estimate the benefit of the intervention. Furthermore, recruiters should not know which assignment (treatment or control group) is next in line. Recruiters who assess eligibility criteria and are aware of the next random allocation may consciously or unconsciously select the healthiest patient to be enrolled in the control group or vice versa. Approaches to randomization that may allow the recruiters to manipulate the assignment include improper use of record numbers (e.g., if all odd numbers were assigned to control group), dates of birth, day of the week, or open lists of random numbers. Examples of bias-free random allocations include centralized randomization (e.g., a central office unaware of subject characteristics allocates group assignments), pharmacy-controlled randomization (assuming that the pharmacist is not recruiting the subjects), and opaque envelopes that are numbered sequentially and sealed.[17]

TABLE 3-3 Additional Resources to Expand Critical Appraisal Skills

The BMJ Publishing Group offers a How to Read a Paper series in both print and online issues of the BMJ (*http://bmj.bmjjournals.com/collections/read.shtml*):
- Papers that report drug trials. *BMJ* 1997;315:480–483; *http://www.bmj.com/cgi/content/ full/315/7106/480*
- Papers that tell you what things cost (economic analyses). *BMJ* 1997;315:596–599; *http://www.bmj.com/cgi/content/full/315/7108/596*
- Papers that summarize other papers (systematic reviews and meta-analyses). *BMJ* 1997;315:672–675; *http://www.bmj.com/cgi/content/full/315/7109/672*
- Papers that go beyond numbers (qualitative research). *BMJ* 1997;315:740–743; *http://www.bmj.com/cgi/content/full/315/7110/740*
- This group also offers a BMJ collection of articles relevant to the critical appraisal of systematic reviews: *http://bmj.bmjjournals.com/collections/ma.htm*

The Centre for Health Evidence provides a series of articles based on the series users' Guides to Evidence-Based Medicine, originally published in *JAMA*:
- Therapy and prevention: *http://www.cche.net/principles/content_therapy.asp*
- Harm: *http://www.cche.net/principles/content_harm.asp*
- Overview articles: *http://www.cche.net/principles/content_overview.asp*
- Clinical decision analyses: *http://www.cche.net/principles/content_d_analysis.asp*
- Clinical practice guidelines: *http://www.cche.net/principles/content_p_guideline.asp*
- Clinical utilization reviews: *http://www.cche.net/principles/content_u_review.asp*
- Outcomes of health service research: *http://www.cche.net/principles/content_v_outcome.asp*
- Quality of life measures: *http://www.cche.net/principles/content_qol.asp*
- Economic analyses: *http://www.cche.net/principles/content_e_analysis.asp*
- Grading health care recommendations: *http://www.cche.net/principles/content_grading.asp*
- Applicability of clinical trials results: *http://www.cche.net/principles/content_results.asp*

The University of Sheffield tutorial provides the basic critical appraisal skills for primary resources but also introduce how to evaluate a Web site: *http://www.shef.ac.uk/scharr/ir/units/critapp/index.htm*

Evaluating the Studies You Find Workshop, produced by the SUNY Health Sciences

Evidence-Based Medicine, is another valuable resource: *http://servers.medlib.hscbklyn.edu/ebm/5toc.htm*

Adapted with permission from Chiquette E, Posey LM. Evidence-Based Pharmacotherapy, 1st ed. Washington, DC: American Pharmacists Association. 2007:95–96.

- *Was the study double-blinded?* To minimize performance bias (systematic differences in the care provided, apart from the intervention being evaluated), the subjects and the clinicians should be unaware of the therapy received. The double-blind method prevents subjects or clinicians from adding any additional treatments (or cointerventions) to one of the groups. For example, clinicians who know that certain patients are receiving the therapy they perceive to be less effective (control group) may opt to check on those patients more often than is required in the study protocol. A third blind can be applied to the outcome assessor (e.g., a statistician or clinician whose role is to measure the outcome) to minimize detection bias (systematic differences in outcome assessment). The necessity for blinding outcome assessors is controversial at this time.
- *Was intention-to-treat analysis performed?* Intention-to-treat analysis means that the results from all subjects randomized in the study were accounted for and attributed to the group to which they were assigned. This strategy minimizes attrition bias and ensures that the known and unknown prognostic factors are kept equally distributed. For example, exclusion of subjects who withdrew early in treatment may bias the comparison because the reasons people withdraw early are often related to prognosis.[18] Excluding early withdrawals from the final analysis may select the subjects most likely to get the best outcome and thereby overestimate the benefit of the intervention.

For a more detailed description of the concepts in critical appraisal, a series of articles published in the *Journal of the American Medical Association (JAMA)* provides a useful tool for practitioners who are evaluating clinical trials.[19–50] These users' guides to the medical literature—developed by The Evidence-Based Medicine Working Group, a group of clinicians at Canada's McMaster University and colleagues across North America—can help to assess the validity of primary studies as well as review articles.

Online materials to support teaching of evidence-based healthcare, including the Users' Guides to Evidence-Based Practice, are now supported through the Centers for Health Evidence at *http://www.cche.net*. Table 3–5 summarizes the key elements to be addressed for each type of evidence to appraise internal validity and usefulness.[19–50]

CONSIDERING CLINICAL RELEVANCE

Once the clinician has gathered all relevant studies, eliminated those that addressed other questions, and identified those with the best methods, one question remains: So what? Also known as the "who cares" test,[51] applying this admittedly crude criterion begins the process of asking oneself, "Will these findings change the way I will treat or prevent this disease in my practice—and specifically for the patient sitting in front of me right now?"

The first step in making this decision is to consider the clinical value of the beneficial outcomes reported. Are the outcomes demonstrating improvements important to the patients? For example, a drug therapy that improves left ventricular ejection fraction (a surrogate end point) does not have the same clinical value as a drug that is shown to decrease mortality or improve functional status (primary end points) in an individual with heart failure.

The usefulness of an intervention depends not only on its efficacy but also on whether the magnitude of the benefit outweighs the risks, costs, and benefits of existing alternative interventions. In this context, the number needed to treat (NNT) and the number needed to harm (NNH) are clinically useful measures. NNT and NNH describe the number of patients who need to be treated and for how long to achieve one favorable or harmful outcome, respectively (Table 3–6 illustrates the values of NNT and NNH). The NNT strategy provides a way to estimate an intervention's impact and tradeoffs and to decide whether this therapy should be implemented.

TABLE 3-4 Metasearch Engines for Web-Based Health Information

Turning Research Into Practice (TRIP)
Web address: *www.update-software.com/trip/about.htm*
Sources: Fifty-eight sites categorized as evidence-based, peer-reviewed journals, guidelines, or other. Sites include top 20 medical journals, evidence-based medicine sites such as Bandolier, Critically Appraised Bank, Cochrane Database of Systematic Reviews, Journal Club on the Web, Evidence-Based Medicine series, guideline and systematic review sites such as SIGN, DARE, NICE, and National Guideline Clearinghouse.
Special features: Updated monthly. Searches use keywords in the title only. Results are displayed by categories: evidence-based, peer-reviewed journals, guidelines, or other.

SUMSearch
Web address: *http://SUMSearch.uthscsa.edu*
Sources: Three Internet sites: The National Library of Medicine, the Database of Abstracts of Reviews of Effectiveness, and the National Guideline Clearinghouse.
Special features: If the first search resulted in too many or not enough hits, SUMSearch uses metasearching and contingency search techniques to query the sites again.

Search.com
Web address: *http://www.search.com*
Sources: Twenty-two Internet sites containing health and medical information. Some of these sites are American College of Physicians Online, Centers for Disease Control and Prevention, *New England Journal of Medicine*, Agency for Healthcare Research and Quality, *Journal of the American Medical Association*, PubMed, Merck, Mayo Clinic, Food and Drug Administration, World Health Organization, WebMD, and Medical Subject Headings (MeSH).
Special features: The site allows customization in choosing search engines and how to display results.

Query Server
Web address: *http://queryserver.com*
Sources: Twelve sites containing health and medical information. These sites are American Health Consultants, American Heart Association, Centers for Disease Control and Prevention, Department of Health and Human Services, Food and Drug Administration, Johns Hopkins Infectious Diseases, Leukemia and Lymphoma Society, MEDLINE, Medscape Clinical Content, Medscape News, National Institutes of Health, National Library of Medicine.
Special features: Results are sorted according to content and/or source.

DARE, Database of Abstracts of Reviews of Effects; NICE, National Institute for Health and Clinical Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

The relative risk reduction (RRR), as a measure of the magnitude of an intervention's effect, can be misleading. It does not discriminate between large and trivial absolute differences between the control and experimental groups. For example, an intervention may result in a 50% risk reduction for the adverse outcome, and this amount of decrease would sound impressive to most clinicians and patients. However, it might represent only a small difference in the risk of a rare event (e.g., 0.2% of patients in a placebo group died compared with 0.1% of patients on active drug). In contrast, a 50% risk reduction might reflect a much more meaningful difference, for instance, when 50% of placebo group died versus 25% of patients in the intervention group (an absolute difference of 25%). The RRR is the same for both examples, but the magnitude of the impact of the intervention is drastically different. The information provided by the RRR is incomplete because it does not take into account the baseline risk of subjects in the trial.

CLINICAL CONTROVERSY

NNT and NNH can be a bit nebulous when it comes to applying these values in clinical situations. *P* values are considered significant routinely when they fall below 0.05, but what is a good NNT in one study may not be so good in another trial. NNT and NNH provide visualizations for how much risk and benefit are present when a group of similar patients—such as those seen by a physician or cared for in a pharmaceutical care clinic—are all treated with a medication or other intervention.

APPLYING THE RESULTS

For every healthcare professional, the ultimate test of which studies are important and which are not comes down to the decision of how to treat each patient. Thus clinical judgment is crucial in assessing the importance of drug-therapy evidence.

Several patient-specific factors must be considered in the final analysis:

- *Compare the patient with those in the study (similar disease state and stage, similar baseline characteristics).* This assessment should ensure that the population studied has a similar disease state and prognostic factors as the patient now being treated. For instance, the results of a trial assessing the mortality benefit of simvastatin in dyslipidemic men with known coronary artery disease would not likely apply to dyslipidemic women with no other coronary risk factors.
- *Consider the patient's baseline risk for the outcome of interest and other potential risks associated with the therapy.* If this patient has a higher baseline risk for the outcome than the population studied, then treatment may yield an even higher benefit. In contrast, if the patient has a lower baseline risk than the population studied, then treatment-associated risks may outweigh the potential benefit. For example, premenopausal women, in general, have a lower cardiovascular mortality risk than do men. Therefore, an intervention shown to prevent cardiovascular mortality in men may result in a smaller benefit in women.
- *Consider the patient's values, beliefs, concerns, and readiness for the intervention.* In addition, healthcare delivery characteristics (cost and accessibility) must be factored in. Although not very long ago healthcare professionals were considered patriarchal figures who directed the patient's treatment, today patients are fully engaged partners in decisions about therapy. The evidence must be discussed and integrated with the specific patient's circumstances to result in successful outcomes.

KEEPING UP TO DATE BY USING EVIDENCE-BASED MEDICINE

4 The same combination of clinical experience and EBM skills that enables healthcare professionals to resolve patient-specific pharmacotherapeutic questions also aids healthcare professionals' continued efforts to keep up to date. The process is the same: (a) recognize information needs (the areas of one's practice), (b) identify literature relevant to clinical practice, (c) critically appraise the evidence for validity and usefulness, and (d) devise a mechanism to implement new evidence in daily practice.

As with human knowledge in general, medical information is growing exponentially. Clinicians have difficulty staying current; a few statistics explain why. The National Library of Medicine contains more than 11 million citations covering nearly 4,500 biomedical journals.[52] The number of citations *doubled* in just 6 years, from 1995 to 2001. Each year, 10,000 RCTs addressing the impact of healthcare interventions are published. Some influence how clinicians practice, others provide preliminary evidence that is either too early to act on or irrelevant to clinical practice, and others are seriously flawed and should not be implemented. Who has time to read it all and separate the good from the bad? A literature-sorting strategy, using the EBM approach, is one solution.

First, the clinician must recognize the areas important in his or her practice (e.g., internal medicine, cardiology, nuclear medicine, nutrition, psychiatry, or pharmacokinetics). Second, scan the literature for clinically relevant studies in that area of interest or practice.

TABLE 3-5 Checklist for Critical Appraisal of Articles Addressing Pharmacotherapeutic Decisions

Therapy

Internal validity
- Was subject's treatment allocation randomized?
- Was the study double blinded?
- Was intention-to-treat analysis performed?
- Was the randomization successful?

Magnitude of the effect
- What was the impact of the treatment?
- How narrow is the 95% confidence interval range?
- Were clinically relevant outcomes considered?

Applicability
- Does this patient fulfill inclusion criteria for the trial?
- Do the treatment benefits outweigh the risks?

Harm

Internal validity
- Were the control subjects similar to the cases?
- Was bias minimized while measuring exposure and outcomes?
- Was length of followup appropriate?
- Does exposure precede the adverse outcome?
- Is there a dose–response relationship?

Magnitude of the effect
- How strong is the association between exposure and outcome?
- How precise is the estimate?
- How many patients must be exposed to the agent to cause an adverse event?

Applicability
- What is the likelihood of harm in my patient?
- What are the consequences of eliminating the agent from my patient's therapy?

Overview, systematic reviews, meta-analysis

Internal validity
- Did the overview clearly state a well-formulated question?
- Were the criteria used to select articles for inclusion appropriate?
- Were all relevant studies included?
- Were included articles critically appraised for quality?
- Was bias minimized in the selection, data extraction, and analysis processes?
- Were all clinically important outcomes considered?
- Were the studies appropriately combined?

Magnitude of the effect
- What is the average effect?
- How precise are the results?

Applicability
- Are this patient's characteristics similar to the subjects included in the studies?
- Do the treatment benefits outweigh the risks?

Practice guidelines

Internal validity
- Were the management options and outcomes clearly specified?
- Was all evidence relevant to each arm of the evidence model sought?
- Were systematic and explicit methods used to identify, select, and combine evidence?
- Were all clinically relevant outcomes evaluated?
- Is the guideline up-to-date?
- Does the guideline clearly present the evidence to support the benefit of following the recommendations?
- Has the guideline been peer reviewed?

Magnitude of the effect
- How strong are the recommendations?
- What is the impact of uncertainty in the evidence on outcomes?

Applicability
- Are the guideline recommendations targeting my practice (e.g., family practice setting vs. endocrinology setting)?
- Is my patient the intended target for this guideline?

Economic analyses

Internal validity
- Were both costs and outcomes evaluated for all strategies considered?
- Were costs and outcomes measured and valued accurately?
- Was the potential impact of uncertainties in the analysis evaluated?
- Was the potential impact of different baseline risk in the treatment population estimated on costs and outcomes?

Magnitude of the effect
- What were the incremental costs and outcomes of each strategy considered?
- Do incremental costs and outcomes vary between selected groups of patients?
- What is the impact of sensitivity analyses on incremental cost?

Applicability
- Do the treatment benefits outweigh the treatment risk and cost?
- Are the results transferable to my practice setting (e.g., similar patient types, similar costs of resources)?

Adapted from Users' Guide Series, references 19 to 50.

TABLE 3-6 Number Needed to Treat and Number Needed to Harm

In this example, the clinical question is whether the addition of clopidogrel to the regimen of a 65-year-old man with unstable angina who is already taking aspirin would prevent death or coronary event? A search of published trials and presented papers at scientific meetings uncovered only one relevant study (*N Engl J Med* 2001;345(7):494–502).

In the trial:
- 12,562 subjects with coronary syndrome were randomized to aspirin alone or aspirin plus clopidogrel.
- On average, patients were followed for 9 months.
- The primary end point was to prevent cardiovascular (CV) death, myocardial infarction (MI), or stroke.

To calculate the number needed to treat (NNT), first calculate the absolute risk reduction (ARR). This is the absolute difference between the event rate in the control group (CER) minus the event rate in the experimental group (EER). The NNT is the inverse of the ARR.

The trial reports that 11.47% of the aspirin-alone group (control group) had MI, stroke, or CV death. In contrast, 9.28% of the aspirin-plus-clopidogrel group (experimental group) had these events.

Control Event Rate (Aspirin-Alone Group)	Experimental Event Rate (Aspirin-Plus-Clopidogrel)	RRR = (CER – EER)/CER	ARR = (CER – EER)	NNT = 1/ARR
11.47%	9.28%	19%	2.19%	46

Thus the NNT is 46. That is, treating 46 patients with unstable angina for 9 months with aspirin with clopidogrel should prevent MI, stroke, or CV death in 1 patient. To balance risks against benefits of an intervention, we can generate a similar number needed to harm to express the risks associated to the intervention.

The trial reports that 2.7% of the aspirin-alone group had major nonfatal bleeding events compared with 3.6% of subjects in the intervention group (aspirin plus clopidogrel).

To calculate the number needed to harm (NNH), first calculate the absolute risk increase (ARI). This is the absolute difference between the event rate in the experimental group (EER) minus the event rate in the control group (CER). The NNH is the inverse of the ARI.

Control Event Rate	Experimental Event Rate	ARI (Absolute Risk Increase)	NNH
2.7%	3.6%	0.9%	111

The NNH is thus 111, meaning that treating 111 patients with both drugs for 9 months would result in 1 major nonfatal bleed. Combining the NNT and NNH and projecting the results to 1,000 patients would lead to this conclusion: This randomized, controlled trial suggests that treating 1,000 individuals with unstable angina with the combination of aspirin plus clopidogrel would prevent 21 patients from having a stroke, MI, or CV death at the cost of 9 major nonfatal bleeding events.

$$\text{Usefulness of Medicine Information} = \frac{\text{Relevance} \times \text{Validity}}{\text{Work Factor}}$$

FIGURE 3-1. In this usefulness formula, *relevance* represents patient-oriented evidence that matters and affects healthcare, *validity* refers to a true estimate of the effect, and *work factor* describes the effort required to review the information.

These are studies addressing clinical outcomes likely to be relevant to clinical practice and possibly change prescribing behaviors, such as those that report the effect of a pharmacotherapy on quality of life, cost-effectiveness, mortality, or morbidity. In contrast, trials addressing the impact of drug therapy on surrogate end points (e.g., biochemical markers) most often are irrelevant to current clinical practice and rarely would result in a change in practice. When in a "keeping up-to-date mode," choose the studies reporting clinically relevant outcomes over those with surrogate end points. Third, critically appraise the evidence for validity and usefulness. When addressing therapeutic efficacy, RCTs are considered the "gold standard" and should be preferred over observational studies for most clinical questions. Scan the abstracts of RCTs for obvious design flaws and size of the effect before appraising further. Shaughnessy et al.[53] have created a formula to help determine the usefulness of medical information (Fig. 3–1). Finally, integrate the new findings into one's daily practice.

If this process seems too labor-intensive for keeping pace with the medical literature, consider an evidence-based abstraction service. These services, which have grown tremendously in the past 10 years, claim to reduce by 98% the amount of clinical literature a clinician needs to read, enabling the busy healthcare professional to concentrate on the 2% that is most methodologically rigorous and useful to the clinician's practice.[54] In general, abstraction services consist of an editorial team that scans dozens of journals, usually organized by specialty. They identify articles of potential clinical relevance, critically appraise the studies, and provide commentary on the quality/validity and clinical significance of the results reported. Table 3–7 presents a selected list of translation journals offering evidence-based abstracts of original research.

TABLE 3-7 Evidence-Based Abstraction Services

ACP Journal Club (*http://www.acponline.org/journals/acpjc/jcmenu.htm*) **Audience:** Internal medicine, primary care **Selection criteria:** Original articles, systematic reviews, English, adult, clinically relevant with important outcomes, randomized controlled trials for treatment questions **Journals scanned:** 26 journals
Bandolier (*http://www.jr2.ox.ac.uk/bandolier/*) **Audience:** Internal medicine **Selection criteria:** Those that look remotely interesting are read, and those that are both interesting and make sense are summarized **Journals scanned:** Each month PubMed and the Cochrane Library are searched for systematic reviews and meta-analyses recently published
Evidence-Based Cardiovascular Medicine (*http://www.harcourt-international.com/journals/ebcm/*) **Audience:** Cardiology (adult and pediatric) **Selection criteria:** Original articles, English, clinically relevant, adult or pediatric, human, randomized, double-blinded, controlled trials **Journals scanned:** 25 journals mostly cardiology specialty journals
Evidence-Based Health Care (*http://www.harcourt-international.com/journals/ebhc/*) **Audience:** Managers **Selection criteria:** Articles providing evidence for decision making; articles that are likely to be widely applicable **Journals scanned:** More than 50 journals mostly with an economics and public health focus
Evidence-Based Medicine (*http://www.evidence-basedmedicine.com*) **Audience:** Internal medicine, general and family practice, surgery, psychiatry, pediatrics, and obstetrics and gynecology **Selection criteria:** Original articles; Cochrane Reviews; randomized, controlled trial or therapeutic efficacy trial; clinically relevant outcomes; 80% followup **Journals scanned:** More than 30 journals
Evidence-Based Mental Health (*http://www.ebmentalhealth.com/*) **Audience:** Mental health clinicians **Selection criteria:** Original articles; Cochrane Reviews; randomized, controlled trials or therapeutic efficacy trials; clinically relevant outcomes; 80% followup **Journals scanned:** Not available
Journal Watch series (*http://www.jwatch.org/*) **Audience:** General medicine, dermatology, cardiology, psychiatry, women's health, emergency medicine, infectious disease, neurology, gastroenterology (specialty Journal Watch for each audience) **Selection criteria:** Not given **Journals scanned:** More than 50 journals
Journal of Family Practice (*http://www.jfp.msu.edu*) **Audience:** Family practice, pharmacists **Selection criteria:** High-quality articles with patient-oriented outcomes that have the greatest potential to change the way that primary care clinicians practice **Journals scanned:** 80 journals
Journal Club on the Web (*http://www.journalclub.org*) **Audience:** Internal medicine **Selection criteria:** Not given **Journals scanned:** *New England Journal of Medicine, Annals of Internal Medicine, Journal of the American Medical Association, The Lancet*

CONCLUSIONS

5 Is EBM realistic? The needed skills for practicing EBM may appear daunting, but once acquired, they can help healthcare professionals to better use available resources and time by knowing how to focus a search and be more critical in what reading and information to integrate into their knowledge base. Several sites have demonstrated that EBM can be incorporated into practice successfully.[55–58]

Why practice EBM? Implementing EBM in a practice provides a framework and the skills to strengthen confidence in pharmacotherapeutic decisions and results in better communication with colleagues involved in the decision-making process. Furthermore, an evidence-based pharmaceutical care plan facilitates dialogue with patients about the rationale for the management decisions. Finally, using EBM principles enables practicing healthcare professionals to update their knowledge continuously.

ABBREVIATIONS

EBM: evidence-based medicine

MI: myocardial infarction

NLM: National Library of Medicine

NNH: number needed to harm

NNT: number needed to treat

PVC: premature ventricular contraction

RCT: randomized, controlled trial

RRR: relative risk reduction

REFERENCES

1. Etminan M, Wright JM, Carleton BC. Evidence-based pharmacotherapy: Review of basic concepts and applications in clinical practice. Ann Pharmacother 1998;32:1193–1200.
2. Swales JD. Evidence-based medicine and hypertension. J Hypertens 1999;17:1511–1516.
3. Mancia G, Zanchetti A. Evidence-based medicine: An educational instrument or a standard for implementation [editorial]? J Hypertens 1999;17:1509–1510.

4. Echt DS, Liebson PR, Mitchell B, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo: The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781–788.
5. Greene HL, Roden DM, Katz RJ, et al. The Cardiac Arrhythmia Suppression Trial: First CAST, then CAST-II. J Am Coll Cardiol 1992;19:894–898.
6. Ryan TJ, Antman EM, Brooks NH, et al. 1999 Update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34:890–911.
7. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1996;28:1328–1428.
8. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605–613.
9. Sackett DL, Richardson SW, Rosenberg W, Haynes BR. Evidence-Based Medicine: How to Practice and Teach EBM. New York: Churchill-Livingstone, 1997.
10. Richardson WS, Wilson MC, Nishikawa J, Hayward RSA. The well-built clinical question: A key to evidence-based decisions [editorial]. ACP J Club 1995;123:A12–A13.
11. Ghosh AK, Ghosh K. Enhance your practice with evidence-based medicine. Patient Care 2000;Feb:32–56.
12. Oxman A, Guyatt GH. The science of reviewing research. Ann N Y Acad Sci 1993;703:125–134.
13. Mulrow CD. The medical review article: State of the science. Ann Intern Med 1987;106:485–488.
14. Mulrow CD. Rationale for systematic reviews. BMJ 1994;309:597–599.
15. Haynes RB, Wilczynski NL, McKibbon KA, et al. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. J Am Med Inform Assoc 1994;1:447–458.
16. Huth EJ. How to Write and Publish Papers in the Medical Sciences, 2d ed. Philadelphia: ISI Press, 1990:56–57.
17. Chalmers TC, Smith H Jr, Blackburn B, et al. A method for assessing the quality of a randomized control trial. Control Clin Trials 1981;2:31–49.
18. Horwitz RI, Viscoli CM, Berkman L, et al. Treatment adherence and risk of death after a myocardial infarction. Lancet 1990;336:542–545.
19. Oxman AD, Sackett DL, Guyatt GH. Users' guides to the medical literature: I. How to get started. The Evidence-Based Medicine Working Group. JAMA 1993;270:2093–2095.
20. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature: II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1993;270:2598–2601.
21. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature: II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1994;271:59–63.
22. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature: III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1994;271:389–391.
23. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature: III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 1994;271:703–707.
24. Levine M, Walter S, Lee H, et al. Users' guides to the medical literature: IV. How to use an article about harm. Evidence-Based Medicine Working Group. JAMA 1994;271:1615–1619.
25. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature: V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 1994;272:234–237.
26. Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature: VI. How to use an overview. Evidence-Based Medicine Working Group. JAMA 1994;272:1367–1371.
27. Richardson WS, Detsky AS. Users' guides to the medical literature: VII. How to use a clinical decision analysis. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1995;273:1292–1295.
28. Richardson WS, Detsky AS. Users' guides to the medical literature: VII. How to use a clinical decision analysis. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1995;273:1610–1613.
29. Hayward RS, Wilson MC, Tunis SR, et al. Users' guides to the medical literature: VIII. How to use clinical practice guidelines. A. Are the recommendations valid? The Evidence-Based Medicine Working Group. JAMA 1995;274:570–574.
30. Wilson MC, Hayward RS, Tunis SR, et al. Users' guides to the medical literature: VIII. How to use clinical practice guidelines. B. What are the recommendations and will they help you in caring for your patients? The Evidence-Based Medicine Working Group. JAMA 1995;274:1630–1632.
31. Guyatt GH, Sackett DL, Sinclair JC, et al. Users' guides to the medical literature: IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995;274:1800–1804.
32. Naylor CD, Guyatt GH. Users' guides to the medical literature: X. How to use an article reporting variations in the outcomes of health services. The Evidence-Based Medicine Working Group. JAMA 1996;275:554–558.
33. Naylor CD, Guyatt GH. Users' guides to the medical literature: XI. How to use an article about a clinical utilization review. Evidence-Based Medicine Working Group. JAMA 1996;275:1435–1439.
34. Guyatt GH, Naylor CD, Juniper E, et al. Users' guides to the medical literature: XII. How to use articles about health-related quality of life. Evidence-Based Medicine Working Group. JAMA 1997;277:1232–1237.
35. Drummond MF, Richardson WS, O'Brien BJ, et al. Users' guides to the medical literature: XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1997;277:1552–1557.
36. O'Brien BJ, Heyland D, Richardson WS, et al. Users' guides to the medical literature: XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1997;277:1802–1806.
37. Dans AL, Dans LF, Guyatt GH, Richardson S. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. JAMA 1998;279:545–549.
38. Richardson WS, Wilson MC, Guyatt GH, et al. Users' guides to the medical literature: XV. How to use an article about disease probability for differential diagnosis. Evidence-Based Medicine Working Group. JAMA 1999;281:1214–1219.
39. Guyatt GH, Sinclair J, Cook DJ, Glasziou P. Users' guides to the medical literature: XVI. How to use a treatment recommendation. Evidence-Based Medicine Working Group and the Cochrane Applicability Methods Working Group. JAMA 1999;281:1836–1843.
40. Barratt A, Irwig L, Glasziou P, et al. Users' guides to the medical literature: XVII. How to use guidelines and recommendations about screening. Evidence-Based Medicine Working Group. JAMA 1999;281:2029–2034.
41. Randolph AG, Haynes RB, Wyatt JC, et al. Users' guides to the medical literature: XVIII. How to use an article evaluating the clinical impact of a computer-based clinical decision support system. JAMA 1999;282:67–74.
42. Bucher HC, Guyatt GH, Cook DJ, et al. Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. Evidence-Based Medicine Working Group. JAMA 1999;282:771–778.
43. McAlister FA, Laupacis A, Wells GA, Sackett DL. Users' guides to the medical literature: XIX. Applying clinical trial results. B. Guidelines for determining whether a drug is exerting (more than) a class effect. JAMA 1999;282:1371–1377.
44. Hunt DL, Jaeschke R, McKibbon KA. Users' guides to the medical literature: XXI. Using electronic health information resources in evidence-based practice. Evidence-Based Medicine Working Group. JAMA 2000;283:1875–1879.
45. McAlister FA, Straus SE, Guyatt GH, Haynes RB. Users' guides to the medical literature: XX. Integrating research evidence with the care of the individual patient. Evidence-Based Medicine Working Group. JAMA 2000;283:2829–2836.
46. McGinn TG, Guyatt GH, Wyer PC, et al. Users' guides to the medical literature: XXII. How to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA 2000;284:79–84.

47. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 2000;284:357–362.
48. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care. B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. JAMA 2000;284:478–482.
49. Richardson WS, Wilson MC, Williams JW Jr, et al. Users' guides to the medical literature: XXIV. How to use an article on the clinical manifestations of disease. Evidence-Based Medicine Working Group. JAMA 2000;284:869–875.
50. Guyatt GH, Haynes RB, Jaeschke RZ, et al. Users' guides to the medical literature: XXV. Evidence-based medicine: Principles for applying the users' guides to patient care. Evidence-Based Medicine Working Group. JAMA 2000;284:1290–1296.
51. Huth EJ. Writing and Publishing in Medicine, 3d ed. Baltimore: Williams & Wilkins, 1999:10–12.
52. PubMed, MEDLINE Retrieval on the World Wide Web. National Library of Medicine, Bethesda, MD. 2004, *http://www.nlm.nih.gov/pubs/factsheets/pubmed.html*.
53. Shaughnessy AF, Slawson DC, Bennet JH. Becoming an information master: A guidebook to the medical information jungle. J Fam Pract 1994;39:484–499.
54. Sackett DL, Haynes RB. 13 steps, 100 people, 1,000,000 thanks. Evid Based Med 1997;2:101–102.
55. Ellis J, Mulligan I, Rower J, Sackett DL. Inpatient general medicine is evidence-based. Lancet 1995;346:407–410.
56. Geddes JR, Game D, Jenkins NE, et al. What proportion of primary psychiatric interventions are based on randomised evidence? Qual Health Care 1996;5:215–217.
57. Gill P, Dowell AC, Neal RP, et al. Evidence-based general practice: A retrospective study of interventions in our training practice. BMJ 1996;312:819–821.
58. Kenny SE, Shankar KR, Rentala R, et al. Evidence-based surgery: Interventions in a regional pediatric surgical unit. Arch Dis Child 1997;76:50–53.