Evidence-Based Medicine

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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-

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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.

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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.8,9 Overall risk for nonfatal MI or coronary death with estrogen therapy does reduce mortality in women with moderate and severe coronary disease.”7

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**

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:

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 question11:

- **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 test 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**
http://www.nlm.nih.gov/healthlit

- 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.ahrq.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

<table>
<thead>
<tr>
<th>Resources</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best Evidence</strong></td>
<td>• All review articles are systematic reviews</td>
<td>• Includes systematic reviews only from the journals scanned by ACP Journal Club and Evidence-Based Medicine</td>
</tr>
<tr>
<td>Electronic version of both American College of Physicians (ACP) Journal Club and Evidence-Based Medicine (<a href="http://hinu.mcmaster.ca/acpj/apc1.htm">http://hinu.mcmaster.ca/acpj/apc1.htm</a>); available on CD-ROM</td>
<td>• Updated every 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Short title includes meta-analysis or review to facilitate identification</td>
<td></td>
</tr>
<tr>
<td><strong>MEDLINE</strong></td>
<td>• Covers more than 4,000 journals</td>
<td>• One-tenth of the citations are indexed as review articles. Even fewer are indexed as systematic reviews.</td>
</tr>
<tr>
<td>Systematic review strategy: (meta-analy$ or metanal$ or metaanaly$).tw. or Meta-Analysis/or meta-analysis (pt) or (quantitativ$ 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.</td>
<td>• Contains 11 million citations</td>
<td></td>
</tr>
<tr>
<td><strong>Cochrane Library</strong></td>
<td>• Most comprehensive collection of systematic reviews</td>
<td>• Limited access; not all libraries subscribe to the Cochrane Library</td>
</tr>
<tr>
<td>Electronic library of high-quality reviews (<a href="http://www.cochrane.org">http://www.cochrane.org</a>); available on CD-ROM.</td>
<td>• Updated every 3 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Abstracts of Cochrane Reviews are available free on the Internet at <a href="http://www.cochrane.org">http://www.cochrane.org</a></td>
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</tr>
<tr>
<td><strong>United Kingdom National Health Services Centre for Reviews and Dissemination (<a href="http://agatha.york.ac.uk/welcome.htm">http://agatha.york.ac.uk/welcome.htm</a>)</strong></td>
<td>• 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</td>
<td>• Significant delay between original publication and entry into the CRD databases</td>
</tr>
<tr>
<td>Includes the Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic evaluation database, and the Health Technology Assessment (HTA) database</td>
<td></td>
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<tr>
<td><strong>Effective Health Care Bulletins (<a href="http://www.york.ac.uk/inst/crd/ehcb.htm">http://www.york.ac.uk/inst/crd/ehcb.htm</a>)</strong></td>
<td>• Reports of systematic reviews produced by NHS Centre for Reviews and Dissemination</td>
<td>• Limited number of reviews</td>
</tr>
</tbody>
</table>
| Part of the UK National Health Service (NHS). Provides guidelines and technology assessments to health care practitioners ([http://nice.org.uk](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 searching using methodologic filters. These filters, based on work by Haynes et al., 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 facilitate identification of the next steps in therapy. 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 the outcome of the intervention (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.

- **Was the trial conducted with a blinded outcome assessor?** To minimize bias, blinding the outcome assessor is necessary. It is important to determine whether the outcome assessor was blinded to the treatment or control group assigned to the patient. If not, the outcome assessor may influence the interpretation of the data.

**ASSESSING VALIDITY**

- **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 the outcome of the intervention (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
The BMJ Publishing Group offers a How to Read a Paper series in both print and online issues of the BMJ (http://bmj.bmjournals.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.bmjournals.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://www.cche.net/principles/content_therapy.asp

| TABLE 3-3 | Additional Resources to Expand Critical Appraisal Skills |

| 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. |

| 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. |


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, 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.
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

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. 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.

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

<table>
<thead>
<tr>
<th>Metasearch Engine</th>
<th>Web Address</th>
<th>Sources</th>
<th>Special Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turning Research Into Practice (TRIP)</td>
<td><a href="http://www.update-software.com/trip/about.htm">web address</a></td>
<td>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 Bandsol, 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.</td>
<td>Updated monthly. Searches use keywords in the title only. Results are displayed by categories: evidence-based, peer-reviewed journals, guidelines, or other.</td>
</tr>
<tr>
<td>SUMSearch</td>
<td><a href="http://SUMSearch.uthscsa.edu">web address</a></td>
<td>Three Internet sites: The National Library of Medicine, the Database of Abstracts of Reviews of Effectiveness, and the National Guideline Clearinghouse.</td>
<td>The first search resulted in too many or not enough hits. SUMSearch uses metasearching and contingency search techniques to query the sites again.</td>
</tr>
<tr>
<td>Search.com</td>
<td><a href="http://www.search.com">web address</a></td>
<td>Twenty-two Internet sites containing health and medical information. 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).</td>
<td>The site allows customization in choosing search engines and how to display results.</td>
</tr>
<tr>
<td>Query Server</td>
<td><a href="http://queryserver.com">web address</a></td>
<td>Twelve sites containing health and medical information. 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.</td>
<td>Results are sorted according to content and/or source.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Control Event Rate (Aspirin-Alone Group)</th>
<th>Experimental Event Rate (Aspirin-Plus-Clopidogrel)</th>
<th>RRR = (CER – EER)/CER</th>
<th>ARR = (CER – EER)</th>
<th>NNT = 1/ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.47%</td>
<td>9.28%</td>
<td>19%</td>
<td>2.19%</td>
<td>46</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Control Event Rate</th>
<th>Experimental Event Rate</th>
<th>ARI (Absolute Risk Increase)</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7%</td>
<td>3.6%</td>
<td>0.9%</td>
<td>111</td>
</tr>
</tbody>
</table>

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.

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SECTION 1 Foundation Issues

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.

### 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.\(^35–38\)

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 pharmacological 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

### REFERENCES


### TABLE 3–7 Evidence-Based Abstraction Services

<table>
<thead>
<tr>
<th>Journals scanned:</th>
<th>Audience:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP Journal Club (<a href="http://www.acponline.org/journals/acpj/cjmenu.htm">http://www.acponline.org/journals/acpj/cjmenu.htm</a>)</td>
<td>Internal medicine, primary care</td>
</tr>
<tr>
<td>Bandolier (<a href="http://www.jr2.ox.ac.uk/bandolier/">http://www.jr2.ox.ac.uk/bandolier/</a>)</td>
<td>Internal medicine</td>
</tr>
<tr>
<td>Evidence-Based Cardiovascular Medicine (<a href="http://www.harcourt-international.com/journals/ecbm/">http://www.harcourt-international.com/journals/ecbm/</a>)</td>
<td>Cardiology (adult and pediatric)</td>
</tr>
<tr>
<td>Evidence-Based Medicine (<a href="http://www.evidence-basedmedicine.com">http://www.evidence-basedmedicine.com</a>)</td>
<td>Internal medicine, general and family practice, surgery, psychiatry, pediatrics, and obstetrics and gynecology</td>
</tr>
<tr>
<td>Evidence-Based Mental Health (<a href="http://www.ebmentalhealth.com/">http://www.ebmentalhealth.com/</a>)</td>
<td>Mental health clinicians</td>
</tr>
<tr>
<td>Journal Watch series (<a href="http://www.jwatch.org/">http://www.jwatch.org/</a>)</td>
<td>General medicine, dermatology, cardiology, psychiatry, women’s health, emergency medicine, infectious disease, neurology, gastroenterology (specialty Journal Watch for each audience)</td>
</tr>
<tr>
<td>Journal of Family Practice (<a href="http://www.jfp.msu.edu">http://www.jfp.msu.edu</a>)</td>
<td>Family practice, pharmacists</td>
</tr>
<tr>
<td>Journal on the Web (<a href="http://www.journalclub.org">http://www.journalclub.org</a>)</td>
<td>Internal medicine</td>
</tr>
<tr>
<td>New England Journal of Medicine, Annals of Internal Medicine, Journal of the American Medical Association, The Lancet</td>
<td>More than 50 journals mostly with an economics and public health focus</td>
</tr>
<tr>
<td>Annals of Internal Medicine, New England Journal of Medicine, The Lancet</td>
<td>More than 50 journals mostly cardiology specialty journals</td>
</tr>
<tr>
<td>J Hypertens 1999;17:1511–1516.</td>
<td>More than 50 journals</td>
</tr>
<tr>
<td>J Hypertens 1999;17:1509–1510.</td>
<td>More than 50 journals</td>
</tr>
</tbody>
</table>

NNT: number needed to treat
PVC: premature ventricular contraction
RCT: randomized, controlled trial
RRR: relative risk reduction

**Usefulness of Medicine Information**

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

**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.


