Evidence-Based Medicine
Elaine Chiquette and L. Michael Posey

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 to implement 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 help keep healthcare practitioners current in their field of expertise.

5. EBM is realistic.

EVIDENCE-BASED MEDICINE: INTRODUCTION

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 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, including college courses and continuing education (e.g., seminars and journals), pharmaceutical representatives, and colleagues, as well as guidelines from committees of healthcare facilities, government 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 in addition, 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 Internet, 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, as defined by Etminan et al., is an approach to decision making whereby clinicians appraise scientific evidence and its strength to support their therapeutic decisions.1

Although few would argue against the necessity for basing clinical decisions on the best possible evidence, considerable controversy 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 are crucial in determining whether the external evidence applies to the patient’s disease and whether it should be integrated in the therapeutic plan. Additionally, 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, to inform clinical decisions. For example, a decision about the accuracy of a diagnostic test is best informed by evidence from a cross-sectional study, not an RCT. A cohort study, not an RCT, is best designed to answer 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 are usually 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 premature 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...
antiarhythmic therapy in patients with frequent PVCs and 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.9

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.”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...

Evidence-based medicine (EBM) is controversial in many ways. Some people believe 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 medical literature, and results of evidence-based studies. For an excellent list of EBM links and training resources, access the Center for Evidence Based Medicine (http://www.cebm.net/).

Comparative Effectiveness Research: A Key Emerging Area in Evidence-Based Medicine

Comparative effectiveness research (CER) is not new, but the American Recovery and Reinvestment Act (ARRA) of 2009 reignited the American interest with an investment of $1.1 billion allocated to the Agency for Healthcare Research and Quality ($300 million), National Institutes of Health ($400 million), and U.S. Department of Health and Human Services ($400 million). CER approach, which is based on EBM principles, is a type of systematic research that compares the effectiveness, benefits, and harm of two or more currently available therapeutic options for a given condition.8 The evidence-based comparative information that results from CER helps answer the question of which treatment or device works best for which patient under which circumstances.

The essence of CER is not only about comparing head to head or indirectly several therapeutic options but in the distinction between efficacy and effectiveness. Efficacy can be addressed in a placebo-controlled RCT, while effectiveness looks at whether the treatment works in real life with all its unexpected and unpredictable chaos. Finally, CER should measure outcomes relevant to patients (both benefit and harm) and be analyzed at the individual and group levels. CER is a methodological approach that allows clinicians to get a step closer to personalized medicine.

For pharmacists, understanding CER findings and their implication to disease management is important, as pharmacists are involved in formulary and individual therapeutic decision making that most commonly involve multiple options.

The Institute of Medicine (www.iom.edu) is an excellent source of additional information regarding definition, standards, and prioritization for CER projects in the United States.

INCORPORATING EVIDENCE-BASED MEDICINE INTO PHARMACOTHERAPEUTIC DECISION MAKING

1. 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:10

   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, such as:

1. Should clopidogrel be prescribed to this 65-year-old man with unstable angina?
2. Is it safe to switch carvedilol to metoprolol in this patient with heart failure?
3. Is sildenafil safe in this patient with diabetes mellitus type 2?

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.11 Using these four elements, the preceding questions can be reframed as follows:

1. 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)?
2. Is metoprolol as effective as carvedilol (comparison of two therapeutic alternatives) to prevent cardiovascular events (outcome) in a patient with low ejection fraction heart failure (patient)?
3. 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 diabetes mellitus type 2 (patient)?
The acronym PICO can be helpful to remember the elements of a well-balanced question:

- **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 become less reliable as the volume and complexity of medical information have grown exponentially. Colleagues may have out-of-date information or be 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, Scientific American Medicine Online, and Clinical Evidence Concise electronic textbooks). As their names suggest, evidence-based clinical guidelines are informed 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.

One website—the National Guideline Clearinghouse (http://www.guideline.gov)—provides links to many evidence-based clinical practice guidelines. For each guideline, this comprehensive database offers a short summary of key attributes, including 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. eTable 4-1 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. 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.

The Cochrane Library represents one of the most comprehensive sources of systematic reviews summarizing evidence about healthcare. More than 9,000 Cochrane reviews are currently available, and another 2,000 reviews were in progress when this chapter was finalized in January 2013. Because new reviews are added quarterly, eventually all areas of healthcare will be covered. The Cochrane Library includes the Database of Abstracts of Reviews

---

### eTable 4-1

**North American Sources of Evidence-Based Clinical Practice Guidelines**

<table>
<thead>
<tr>
<th>Source</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Guideline Clearinghouse (NGC) (<a href="http://www.guideline.gov">www.guideline.gov</a>)</td>
<td>- 3,817 guideline summaries&lt;br&gt;- Weekly e-mail alerts&lt;br&gt;- Advanced search queries based on guideline attributes, side-by-side comparison of guidelines&lt;br&gt;- Annotated bibliography of resources relevant to guideline methodology&lt;br&gt;- Palm-based PDA downloads&lt;br&gt;- FDA advisories&lt;br&gt;- E-mail alerts (RSS feeds)</td>
</tr>
<tr>
<td>Agency for Healthcare Research and Quality’s Evidence-Based Practice Centers (AHRQ EPCs) (<a href="http://www.ahrq.gov/clinic/epcix.htm">http://www.ahrq.gov/clinic/epcix.htm</a>)</td>
<td>- More than 200 evidence reports and technology assessments&lt;br&gt;- Full text available&lt;br&gt;- E-mail alerts</td>
</tr>
</tbody>
</table>

FDA, U.S. Food and Drug Administration; PDA, personal digital assistant.
of Effectiveness, which contains about 21,000 structured abstracts of good quality, published reviews about the effectiveness of health interventions. eTable 4-2 lists accessible sources of systematic reviews and provides a search strategy developed by librarians at McMaster University to efficiently locate systematic reviews and meta-analyses on MEDLINE.\(^{16}\)

**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.

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.,\(^{16}\) 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. eTable 4-3 describes the specifics of new metasearch engines available to search for Internet-based health information.

### eTable 4-2 Selected Resources for Systematic Reviews

<table>
<thead>
<tr>
<th>Resources</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE (<a href="http://www.pubmed.gov">www.pubmed.gov</a>)</td>
<td>• Covers more than 5,000 journals&lt;br&gt;• Contains 22 million citations&lt;br&gt;• Includes several filters for more efficient searches&lt;br&gt;A series of video tutorials can be found at: <a href="http://www.nlm.nih.gov/bsd/disted/pubmed.html">http://www.nlm.nih.gov/bsd/disted/pubmed.html</a></td>
<td>• Despite the availability of filters created to identify systematic reviews, several researchers have reported that using these filters may still result in relevant studies being missed. This is particularly true for older studies that may not have been as well indexed.</td>
</tr>
<tr>
<td>Cochrane Library (<a href="http://www.cochrane.org">http://www.cochrane.org</a>)</td>
<td>• Most comprehensive collection of systematic reviews&lt;br&gt;• Updated every 3 months&lt;br&gt;• Podcasts and journal clubs, e-mail alerts added&lt;br&gt;• Abstracts of Cochrane Reviews are available free on the Web at <a href="http://www.cochrane.org">http://www.cochrane.org</a></td>
<td>• Limited access; not all libraries subscribe to the Cochrane Library&lt;br&gt;• Does not cover all disease states, main focus is on treatment</td>
</tr>
<tr>
<td>United Kingdom National Health Services Centre for Reviews and Dissemination (CRD) (<a href="http://www.york.ac.uk/inst/crd">http://www.york.ac.uk/inst/crd</a>)</td>
<td>• The database includes more than 48,000 abstracts of good-quality systematic reviews, economic analyses, and technology assessments. The records included in the database are scored for quality. It includes free e-mail alerts.</td>
<td>• Significant delay between original publication and entry into the CRD databases</td>
</tr>
<tr>
<td>National Institute for Clinical Excellence (<a href="http://nice.org.uk">http://nice.org.uk</a>)</td>
<td>• Follows Cochrane methodology to develop technology assessments: Includes cost-effectiveness analyses for drug therapies</td>
<td>• Limited number of guidelines and assessments available</td>
</tr>
</tbody>
</table>

### eTable 4-3 Metasearch Engines for Web-Based Health Information

#### Turning Research into Practice (TRIP)

**Web address:** [http://www.tripdatabase.com/](http://www.tripdatabase.com/)

**Sources:** This metasearch engine includes 150 sources categorized as evidence-based, peer-reviewed journals, guidelines, or other. Sites include top medical journals, access to the millions of articles in MEDLINE, 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.

#### Query Server

**Web address:** [http://queryserver.dataware.com/health.htm](http://queryserver.dataware.com/health.htm)

**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. Also includes [http://www.clinicaltrial.gov database](http://www.clinicaltrial.gov).

**Special features:** Results are sorted according to content and/or source.

---

DARE, Database of Abstracts of Reviews of Effectiveness; NICE, National Institute for Health and Care Excellence; SIGN, Scottish Intercollegiate Guidelines Network.
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.17

ASSESSING VALIDITY

3 The external validity refers to applicability and generalization and is outlined later in the section called Applying the Results. 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 eTable 4-4 for additional resources on critical appraisal), here are three questions that must be answered in assessing the internal validity of an RCT:

1. 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 the control group), dates of birth, day of the week, or open lists of random numbers. Examples of bias-free random allocations include centralized randomization (assuming that the pharmacist is not recruiting the subjects), and opaque envelopes that are numbered sequentially and sealed.18

2. 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 contraindications) 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.

3. 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.19 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.

eTable 4-4 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:
- Papers that tell you what things cost (economic analyses). BMJ 1997;315:596.
- Papers that summarize other papers (systematic reviews and meta-analyses). BMJ 1997;315:672–675.

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.chc.net/text/usersguides/therapy.asp
- Harm: http://www.cche.net/text/usersguides/harm.asp
- Overview articles: http://www.cche.net/text/usersguides/overview.asp
- Clinical decision analyses: http://www.cche.net/text/usersguides/decision.asp
- Clinical practice guidelines: http://www.cche.net/text/usersguides/guideline.asp
- Clinical utilization reviews: http://www.cche.net/text/usersguides/review.asp
- Outcomes of health service research: http://www.cche.net/text/usersguides/outcomes.asp
- Quality of life measures: http://www.cche.net/text/usersguides/life.asp
- Economic analyses: http://www.cche.net/text/usersguides/economic.asp
- Grading healthcare recommendations: http://www.cche.net/text/usersguides/recommend.asp

Deflini.org was cofounded by Michael Stuart, MD, and Sheri Ann Strite. Their mission is to improve healthcare quality and use of resources by educating the decision makers on how to best apply EBM practice. The site includes online tutorials for critical appraisal and much more: http://www.deflini.org/page_Good_EBM_Tips.htm

The Center for Evidence-Based Medicine offers a collection of critical appraisal worksheets for randomized controlled trials, systematic reviews, and other study design: http://kctlearninghouse.ca/cem/teaching/worksheets.
For a more detailed description of the concepts in critical appraisal, a series of articles published in the *Journal of the American Medical Association* (see eTable 4–4) provides a useful tool for practitioners who are evaluating clinical trials.20–52 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. eTable 4-5 summarizes the key elements to be addressed for each type of evidence to appraise internal validity and usefulness.20–52

### Understanding a Network Meta-Analysis

A traditional meta-analysis quantitatively combines RCTs evaluating the efficacy and safety of one intervention compared with placebo (or a similar active comparator) to obtain an overall estimate of the magnitude of the intervention’s effect (benefit or harm). For clinical questions where many treatment options already exist, the practitioner’s most common information need

<table>
<thead>
<tr>
<th>eTable 4-5</th>
<th>Checklist for Critical Appraisal of Articles Addressing Pharmacotherapeutic Decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapy</strong></td>
<td><strong>Magnitude of the effect</strong></td>
</tr>
<tr>
<td>Internal validity</td>
<td>• Is the treatment network includes sufficient number of studies?</td>
</tr>
<tr>
<td>• Was subject’s treatment allocation randomized?</td>
<td></td>
</tr>
<tr>
<td>• Was the study double blinded?</td>
<td></td>
</tr>
<tr>
<td>• Was intention-to-treat analysis performed?</td>
<td></td>
</tr>
<tr>
<td>• Was the randomization successful?</td>
<td></td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td>• Were all potential treatment options considered to be relevant to my patient?</td>
</tr>
<tr>
<td>• Does this patient fulfill inclusion criteria for the trial?</td>
<td></td>
</tr>
<tr>
<td>• Do the treatment benefits outweigh the risks?</td>
<td></td>
</tr>
<tr>
<td><strong>Harm</strong></td>
<td>• Were the relevant patient centered outcomes included in the analysis?</td>
</tr>
<tr>
<td>Internal validity</td>
<td>• What is the impact of uncertainty in the evidence on outcomes?</td>
</tr>
<tr>
<td>• Were the control subjects similar to the cases?</td>
<td></td>
</tr>
<tr>
<td>• Was bias minimized while measuring exposure and outcomes?</td>
<td></td>
</tr>
<tr>
<td>• Was length of follow-up appropriate?</td>
<td></td>
</tr>
<tr>
<td>• Does exposure precede the adverse outcome?</td>
<td></td>
</tr>
<tr>
<td>• Is there a dose–response relationship?</td>
<td></td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td>• Are the guideline recommendations targeting my practice (e.g., family practice setting vs. endocrinology setting)?</td>
</tr>
<tr>
<td>• What is the likelihood of harm in my patient?</td>
<td></td>
</tr>
<tr>
<td>• What are the consequences of eliminating the agent from my patient’s therapy?</td>
<td></td>
</tr>
<tr>
<td><strong>Overview, systematic reviews, meta-analysis</strong></td>
<td>• Is my patient the intended target for this guideline?</td>
</tr>
<tr>
<td>Internal validity</td>
<td>• Were both costs and outcomes evaluated for all strategies considered?</td>
</tr>
<tr>
<td>• Did the overview clearly state a well-formulated question?</td>
<td></td>
</tr>
<tr>
<td>• Were the criteria used to select articles for inclusion appropriate?</td>
<td></td>
</tr>
<tr>
<td>• Were all relevant studies included?</td>
<td></td>
</tr>
<tr>
<td>• Were included articles critically appraised for quality?</td>
<td></td>
</tr>
<tr>
<td>• Was bias minimized in the selection, data extraction, and analysis processes?</td>
<td></td>
</tr>
<tr>
<td>• Were all clinically important outcomes considered?</td>
<td></td>
</tr>
<tr>
<td>• Were the studies appropriately combined?</td>
<td></td>
</tr>
<tr>
<td><strong>Magnitude of the effect</strong></td>
<td>• What is the impact of sensitivity analyses on incremental cost?</td>
</tr>
<tr>
<td>• How precise are the results?</td>
<td></td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td>• Do incremental costs and outcomes vary between selected groups of patients?</td>
</tr>
<tr>
<td>• Are this patient’s characteristics similar to the subjects included in the studies?</td>
<td></td>
</tr>
<tr>
<td><strong>Network meta-analysis (mixed treatment comparison [MTC] meta-analysis)</strong></td>
<td>• What is the impact of uncertainty in the evidence on outcomes?</td>
</tr>
<tr>
<td>Internal validity</td>
<td>• Are the guideline recommendations targeting my practice (e.g., family practice setting vs. endocrinology setting)?</td>
</tr>
<tr>
<td>• Did the overview clearly state a well-formulated question?</td>
<td></td>
</tr>
<tr>
<td>• Were the criteria used to select studies for inclusion appropriate?</td>
<td></td>
</tr>
<tr>
<td>• Were the studies similar in study population, interventions, and outcomes?</td>
<td></td>
</tr>
<tr>
<td>• Were the studies similar in design, quality, and conduct?</td>
<td></td>
</tr>
<tr>
<td>• Were all potential treatment options considered?</td>
<td></td>
</tr>
<tr>
<td>• Were all relevant studies included?</td>
<td></td>
</tr>
<tr>
<td>• Were included studies individually critically appraised for quality?</td>
<td></td>
</tr>
<tr>
<td>• Was bias minimized in the selection, data extraction, and analysis processes?</td>
<td></td>
</tr>
<tr>
<td>• Was a risk-of-bias assessment performed?</td>
<td></td>
</tr>
<tr>
<td>• Were all clinically important outcomes considered?</td>
<td></td>
</tr>
<tr>
<td>• Were the studies appropriately combined?</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Users’ Guide Series (references 20 to 52).
is to rank the different option’s benefits and harms to choose the best treatment.

Head-to-head RCTs, comparing simultaneously the different alternative therapies, are the preferred evidence. However, these studies are costly and most often inexistent. For example, it may not be possible or economically reasonable to compare the cardiovascular benefits of all statins in one rigorous RCT.

To rank the value of individual agents within the same class of drugs like statins, a network meta-analysis or mixed-treatment comparison (MTC) meta-analysis may be a better approach. The network meta-analysis synthesizes and ranks relative efficacy or safety of a particular intervention versus competing interventions in the absence of strong evidence from head-to-head trials. The value of network or MTC meta-analysis is debated, as it adds additional assumptions and is more subject to error than a traditional meta-analysis, but it is growing in popularity in this era of CER.

eFigure 4-1 compares the traditional meta-analysis with a network meta-analysis. Network meta-analyses span from simple adjusted (anchored) indirect comparisons to more complex multi-treatment direct and indirect comparisons. A full methodology and critical appraisal discussion of network meta-analyses is beyond the scope of this chapter. Guyatt et al. recently published a review to guide the critical appraisal, interpretation, and application of network meta-analyses.35

The three-question internal validity assessment for a network meta-analysis is very similar to a traditional meta-analysis:

1. Were the relevant studies included?
2. Were included studies critically appraised for quality?
3. Was bias minimized in the conduct of the meta-analysis?

Similarly to traditional meta-analysis, the question of whether the studies were appropriately combined applies to network meta-analyses. Two main factors determine appropriate combinability. First, the studies included should have fairly similar interventions (comparable doses, duration of treatment), populations (similar inclusion criteria, baseline risk), and outcomes (similar definition and measurement of outcome) to consider combining them. Second, what is called heterogeneity in traditional meta-analysis is called inconsistency or incoherence in network meta-analysis.

Inconsistency measures variation among estimates, similar to heterogeneity in traditional meta-analysis. The MTC meta-analysis includes direct (head-to-head comparisons between treatments) and indirect comparisons allowing for testing whether the results are coherent between direct and indirect studies. When incoherence or inconsistency is present, the authors should explore whether the difference is caused by clinical or methodological variation between studies. The investigation of incoherence is important as it may suggest subpopulation efficacy and/or safety differences and/or could be a reason for not combining studies.


### 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...
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.

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.

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 plus 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.

The NNH is thus 111, meaning that treating 111 patients with both drugs for 9 months would result in one 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 nine major nonfatal bleeding events.

The number needed to treat (NNT) and the number needed to harm (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:

1. **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 example, 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.
2. 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 men. Therefore, an intervention shown to prevent cardiovascular mortality in men may result in a smaller benefit in women.

3. 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 patient’s specific 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 22 million citations covering more than 5,000 biomedical journals. 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. These are studies addressing clinical outcomes likely to be relevant to clinical practice and possibly change prescribing behavior, 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) are most often 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. have created a formula to help determine the usefulness of medical information (eFig. 4-2). Finally, integrate the new findings into one’s daily practice.

**CONCLUSIONS**

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.

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 management decisions. Finally, using EBM principles enables practicing healthcare professionals to update their knowledge continuously.

**eFIGURE 4-2** 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.

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 the amount of clinical literature a clinician needs to read by 98%, enabling the busy healthcare professional to concentrate on the 2% that is most methodologically rigorous and useful to the clinician’s practice. 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. eTable 4-7 presents a selected list of translation journals offering evidence-based abstracts of original research.

**eTABLE 4-7** Evidence-Based Abstraction Services

<table>
<thead>
<tr>
<th>Service Name</th>
<th>Audience</th>
<th>Journal Categories</th>
<th>Selection Criteria</th>
<th>Journals Scanned</th>
<th>Additional Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP journal club</td>
<td>Internal medicine, primary care</td>
<td>Original articles, systematic reviews, English, adult, clinically relevant with important outcomes, randomized controlled trials for treatment questions</td>
<td>100 clinical journals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence-based medicine</td>
<td>Internal medicine and primary care</td>
<td>Original articles, systematic reviews, randomized, controlled trial or therapeutic efficacy trial, clinically relevant outcomes, 80% follow-up</td>
<td>More than 100 journals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Journal watch series</td>
<td>General medicine, dermatology, cardiology, psychiatry, women’s health, emergency medicine, infectious disease, neurology, gastroenterology, oncology/hematology, pediatrics (specialty Journal Watch for each audience)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNN Pharmacotherapy line</td>
<td>Pharmacists (internal medicine and primary care)</td>
<td></td>
<td>Not given</td>
<td>More than 300 journals</td>
<td></td>
</tr>
<tr>
<td>PPNN Pharmacotherapy line</td>
<td>Major medical weekly journals and the top publications in internal medicine, cardiology, infectious diseases, psychiatry, neurology, rheumatology, pharmacotherapy, pharmacy practice, pediatrics, and geriatrics.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ABBREVIATIONS

ARRA  American Recovery and Reinvestment Act of 2009
CAD  coronary artery disease
CER  comparative effectiveness research
EBM  evidence-based medicine
ISPOR  International Society for Pharmacoeconomics and Outcomes Research
MeSH  Medical Subject Headings
MI  myocardial infarction
MTC  mixed-treatment comparison
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

22. 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, PMID:8258890.
29. Richardson WS, Detcky 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


