

EVIDENCE BASED HEALTH CARE

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Chapter Overview

Evidence-based healthcare is a concept that applies epidemiological principles in clinical decision making. Evidence-based medicine is not a substitute for clinical decisionmaking which doctors must make in caring patients as individuals. The promise of evidence-based healthcare lies in reducing unnecessary care, as well as reducing morbidity and mortality from improper or ineffective tests and treatments.

Objectives

On completion of this chapter, the reader should be able to:

1. Understand the hierarchy of evidence for evidence-based healthcare.
2. Generate a focused question for evidence-based inquiry.
3. Identify and utilize sources of evidence.
4. Evaluate published literature for pertinent data to qualitatively assess studies of diagnostic testing, treatment and prognosis.
5. Explain and calculate absolute risk reduction, absolute risk increase, number-needed-to-treat, number-needed-to-harm , relative risk and odds ratio.
6. Understand the limitations of evidence-based analysis of research and some of the ethical issues underlying evidence-based patient case management.

What is Evidence Based Health Care?

The United States healthcare system is viewed as a system under pressure. Healthcare costs are escalating at an alarming rate. Spending for healthcare nationally accounts for an estimated 16.6 percent of the Gross Domestic Product. Half of the growth in these costs is due to inflation alone.[1] At the same time, concerns over medical errors leave some questioning the quality and suitability of care that is being delivered. One survey suggests that physicians-in-training had disclosed medical errors to their patients less than half the time.[2] Patients and providers alike are looking for solutions to ensure that healthcare is provided in a safe and rational manner; evidence-based medicine may be part of the answer.

Evidence-based healthcare has been defined in many ways. One definition is “a systematic approach to the acquisition, appraisal and application of research evidence to guide healthcare decisions.”[3] The term more often used is “evidence-based medicine”, but evidence-based “healthcare” reflects the broad application of evidence-based strategies to healthcare professions beyond medicine. There are several evidence-based journals devoted to non-physicians as well as medical specialties (for example, nursing, dentistry and eye care).

Evidence-based healthcare is a process to learn from the work of others by (hopefully) identifying the safest and most effective options for managing a particular patient’s

ailment. Use of evidence-based medicine procedures is not an end in itself. Appropriate management of a patient requires sound clinical judgment and reliance upon prior personal "clinical wisdom" to choose the right course of action. Judgment requires determining whether the available evidence is relevant to the patient's specific circumstances and values.[4]

The evidence-based medicine approach requires certain skills to manage the literature and process information. These can be summarized as *Acquire , Appraise, Apply*.[3]

Aquire

Acquiring the information begins with posing a relevant and focused clinical question. Clinical questions usually pertain to diagnosis, treatment, prognosis or harm. The scope of the question is phrased in terms of the *population* of interest, the "*exposure*" in question and the *outcome* expected. Using the population, exposure and outcome model not only provides a versatile template for constructing focused questions, it also makes it easier to find relevant literature as some databases classify journal articles by population, exposure and outcome.[3]

Clinical Pearl
The clinical question should be phrased in terms of the target population, the test or treatment considered, and the desired outcome.

It is vital that the focused question be properly constructed. A question that is too vague, broad or complex hinders acquisition within the framework of evidence-based medicine. For example, if one wished to create a focused question of diagnosis, the generic form of the question might be: "Among patients with a certain condition (the "population"), how accurate is a certain test (the "exposure"), in diagnosing a disease (the "outcome")?[3] An example of this could be: "Among patients aged 70 years or older, how accurate is tonometry in diagnosing glaucoma?"

Once the focused question has been formulated, the information must then be sought and retrieved. Online searches of databases such as the National Library of Medicine's Medline system (http://www.ncbi.nlm.nih.gov/PubMed/) are one such place. Using search terms relating to the population, exposure and outcome in question provide direction toward the evidence contained in journal articles. Special search functions can limit the search to particular types of articles (population age, study type, etc) that are most appropriate to evidence-based practice. Abstracts can viewed at no charge. Some full text articles are available free of charge from publishers and other resources. A good number of articles, particularly those most often cited, are available (with diligent searching) online and free of charge.[5] Other journals charge a fee for the full text article, but in 2010 the U.S. Federal government will begin requiring all research articles funded in whole or in part by the U.S. to be offered for free. For others, retrieving articles often requires a visit to the nearest biomedical library access to inter-library loan services available through academic libraries or specialized libraries such as the International

Library and Museum of Optometry (which is affiliated with the American Optometric Association).

Retrieved articles need to be appraised on the basis of directness, validity and results.[3] A clinical research article published in a journal will have its own focused question which is answered by the article. To evaluate directness is to evaluate how well the journal article's focused question matches the focused question that is undergoing evidence-based inquiry. Sometimes a single article asks the same essential question the clinician is asking on behalf of his or her patient. Other questions may be more complex or not yet asked, and a number of articles may need to be evaluated to build the "whole picture." One must resist the temptation to take compelling evidence from an article and apply it as a "general rule" for all patients. It is important to assess applicability to individual patients and populations. Validity of an article is reflected by the quality of the study design and whether or not the study may lend itself to certain types of research biases (biases will be discussed below). The evidence must then be examined to see how it applies to individual patients whose care relies upon the answers to the focused question. Results are the data-driven conclusions that comprise the "evidence" in the article. Evidence-based medicine, by nature, is data-driven. The statistical analysis involved in evidence-based medicine can easily overwhelm the reader. Hopefully, by learning key statistical principles, the clinician will see the payoff when an actual "answer" can be provided when a patient asks, "Doctor, what are my chances?"

Appraise

JUDGING THE QUALITY OF MEDICAL EVIDENCE

The fact that a manuscript appears in a publication does not always imply that it contains conclusions or recommendations of high quality. Published articles can take several forms and evidence-based analysis proposes a hierarchy for assessing the "quality" of the evidence contained in each article. Some studies are undertaken under more rigorous conditions than others. The aim of pursuing some types of studies in favor of others is to maximize the statistical validity and minimize problems which can compromise the data, such as bias.

The knowledge base is constantly evolving as new publications appear in print utilizing new populations and techniques to answer important clinical questions. Because research and "current understanding" of disease processes is so fluid, some people (with tongue-in-cheek) suggest burning your traditional textbooks in favor of embracing alternative information resources.[4] Instead of textbooks, it is recommended that evidence be gleaned from research published in peer-reviewed journals.

CHARACTERISTICS OF TYPES OF RESEARCH

Published research is categorized as either hypothesis-generating or hypothesis-tested research.[6] Hypothesis-generating research consists of reviews, case reports, suspected patterns, predictions, or anecdotal reports that can inspire theories or ideas for preventing or managing illness or disease. These ideas can then be tested to see whether they are safe and effective by hypothesis-tested research.

There are two types of research that can test a hypothesis: observational and experimental. Observational research analyzes data derived from observing a population or group of patients. Observational data can be extracted from existing patient records, interviews or surveys of patients or other qualitative studies. Experimental studies entail a structured process whereby an intervention is introduced into a group of subjects and the subjects are monitored to find a relationship between the intervention and the outcome for those patients. Data is also collected from subjects who are not exposed to the intervention and this data can be compared to the data from the subjects who are exposed to test whether there may be a causal relationship between exposure and outcome.

Study design is more thoroughly discussed in the chapter "Putting Research into Clinical Practice" by Jones-Jordan and Hoppe. Briefly, evidence-based analysis proposes a hierarchy of evidence, where higher ranks are assigned to study designs that are generally less susceptible to bias and misinterpretation.[7] The rankings are as follows:[8, 9]

I (highest)	randomized controlled trials
II-1	non-randomized controlled trials
II-2	cohort studies or case-control studies
II-3	comparisons between times and places, or dramatic results from uncontrolled experiments
III (lowest)	descriptive studies, case reports, expert opinion or reports from expert committees

A randomized controlled trial is a "superior" form of research which employs controls and strict protocols. Randomized control trials create an experimental group and a control group of subjects. Assignment of subjects to the groups is performed in a randomized fashion. The experimental group is exposed to an "agent" of interest to determine whether the agent results in different outcomes compared to the control group.[10] The best clinical trials are double masked or blinded meaning that neither the subjects nor the examiners know which group subjects are in. The strength of this design is that there should be nothing different (except by chance) between the groups except the exposure of interest. There are some weaknesses to randomized control trials. Because so much weight is placed on randomized control trials, if no "adverse" results are found, the "upside" of the therapy may appear greater than it truly is (a "halo" effect of sorts). If the trial is too short to detect a problem or identify a beneficial effect, a false conclusion of safety or inefficacy may result, respectively. Adverse effects that are rare or unexpected tend not to be detected. This often is due to the fact that these adverse effects need special tests to detect them – tests not typical in a routine battery of tests used in monitoring the therapy and not related to these adverse effects.[11]

A cohort study is similar to a randomized control trial, but is more "passive" in nature and lacks the controls characteristic of randomized control trials. A cohort study tracks

a group of patients with defined exposures and observes outcomes in the future.[10] Case-control studies define the outcome first (case group and control group); then it works backward to measure exposures. Cohort studies are usually prospective. Case-control studies are usually retrospective.

Although it has been widely believed that control trials are categorically superior to "observational" cohort or case-control studies, one article demonstrates that well-performed observational studies are as important as controlled trial studies.[8]

Descriptive studies have their place for reporting new or unexpected events or potential relationships.. Being smaller in size than randomized control trials, they can yield results in less time and at less cost.[11] Perhaps most importantly, descriptive studies provide inspiration for investigating clinical questions through experimental research. For example, published case reports and other descriptive studies generated widespread concern about and further research into the effects of sildenafil (Viagra®) and optic neuropathy.[12, 13]

Another important type of publication is the systematic review. A systematic review is "a summary of the medical literature that uses explicit methods to systematically search, critically appraise, and synthesize the world literature on a specific issue."[4] Systematic reviews use existing studies, such as randomized controlled trials, and critically appraise all relevant data. Such reviews are also referred as "secondary reviews" of the "primary" research (such as the controlled trials). Raters of clinical evidence place the systematic reviews at the apex of the hierarchy of evidence.

Databases such as the Cochrane Database are useful resources tailored to meet the needs of clinicians in search of evidence. The Cochrane Collaboration is an international organization that produces and disseminates systematic reviews and promotes use of evidence-based clinical care. Available at www.cochrane.org, the Cochrane Library and Database are accessible free of charge in some countries. According to the Cochrane website, reviewers who create the systematic reviews number over 11,000 and represent over 90 countries. The Collaboration states that they support any person (consumer or health professional) to participate in the writing of a systematic review, regardless of their background or training. Safeguards are in place to minimize the risk of biases and handle situations where conflicts of interest may arise. Currently in the United States, only residents of Wyoming may access the library of evidence-based reviews free of charge. Individuals or institutions may purchase licenses for access. Abstracts and summaries of the Cochrane Reviews are available free of charge to all on the Cochrane website. Other organizations have systematic reviews available online, such as the "Clinical Evidence" webpage hosted by the *British Medical Journal*, accessible at http://clinicalevidence.bmj.com.

Systematic reviews, such as those developed and disseminated by the Cochrane Collaboration, do not come without a price. It is estimated that the time and direct expenses incurred by the reviewers who read the literature and write the review costs about $50,000 for each review.[14] Given the hundreds of diseases and treatments

possible in the sum of medical care, the total costs for performing systematic reviews for the scope of all ailments would be staggering.

Tools to evaluate research with specific criteria are available from numerous sources, many of them online. For example, the Centre for Evidence-Based Medicine, accessible at www.cebm.net, has downloadable "critical appraisal sheets" to judge the quality of various types of clinical research. One very comprehensive clearinghouse of information is *Netting the Evidence*, accessible at http://www.shef.ac.uk/scharr/ir/netting/.

One specific type of systematic review is the meta-analysis and is considered to be a more quantitative review than other review articles might be. A meta-analysis will pool the results of multiple published studies all of which study the same disease or treatment in question. The "strength in numbers" achieved by pooling all of the data from multiple articles is distilled by formal statistical methods and a clearer "big picture" can be obtained – a clearer picture than any individual study from the pool might show. Pooled analysis can reveal greater benefit for a treatment, increase generalizability of a study across the population, and identify subgroups of patients who might respond favorably (or unfavorably) to a particular treatment.[11] Care must be exercised, however, to include only studies of high quality in the pool. Each study must meet the same preset criteria such as minimum sample size, equivalent measurement techniques, masked subjects and examiners, etc. Bad studies could dilute both the "good news" and the "bad news" from the good studies. As such, publication bias (discussed later) can also be another potential source of problems. Meta-analyses remain a popular method of examining data despite their vulnerabilities.

EVALUATING EVIDENCE OF STUDIES IN DIAGNOSIS

Diagnostic tests are ordered for several reasons: to establish a diagnosis in a patient with signs and symptoms, to screen for disease among asymptomatic patients,to provide prognostic information in patients with a confirmed disease, and to monitor patient status during ongoing therapy.[7]

A patient will present with a complaint/concern, a history, as well as signs and symptoms which will lead the doctor to create a list of possible diagnoses. The tentative diagnoses can help generate a list of tests which could be run to ultimately lead to a probable diagnosis. Each tentative diagnosis on the list has a *pretest probability*, or likelihood of disease *before* any tests are run. After performing a diagnostic test, the results will increase the probability of some diagnoses and decrease suspicions of other diagnoses. *Post-test probability* can be calculated to estimate likelihood of a disease *after* a test is run. Keep in mind that a "test" does not have to be performed by a clinical laboratory or radiology department. A test can also be an item of history, an examination procedure (for example, keratometry to measure corneal curvature), or an activity performed during examination (for example, a psychological inventory to diagnose autism).

Recall from the chapter on screening, the following 2x2 square describing sensitivity and specificity of a screening test:

	(+) Disease	(-) Disease
Positive test	A	B
Negative test	C	D

Sensitivity = True Positive/(True Positive + False Negative) = a/(a+c)

Specificity =True Negative/(True Negative + False Positive) = d/(d+b)

Positive Predictive Value=True Positive/(True Positive + False Positive) = a/(a+b)*

Negative Predictive Value=True Negative/(True Negative +False Negative) = d/(d+c)*

* These abbreviated formulas only work when the prevalence of disease is high (>12%)

Sensitivity and specificity can also be applied to clinical diagnostic tests. These two statistics are not influenced by the prevalence of the disease and they "look backwards" by looking at proportions of patients already tested.[15] Sensitivity is a measure of the test- what percent of patients with disease are caught. Specificity is the percent of patients without disease who are categorized as healthy. But, doctors order tests to determine the likelihood of disease in someone who is about to be tested. To "look forward", statistical values such as positive and negative predictive values are helpful. Predictive values measure the patient. Positive and negative predictive values indicate the probability that a test will make a correct diagnosis.[15] Positive predictive value is simply the probability that a person who tests positive actually has the disease. Negative predictive value is the probability that a person who tests negative does not have the disease.

Likelihood Ratio

The likelihood ratio is the ratio of the two likelihoods. The likelihood ratio for positive test results is equal to: likelihood of positive test result with disease / likelihood of positive test result without disease. This can also be expressed as: sensitivity / (1-specificity).

Similarly, the likelihood ratio for negative test results equals likelihood of negative test result with disease / likelihood of negative test result without disease. This can also be expressed as: (1-sensitivity) / specificity.

Nomograms have been developed to aid in calculating likelihood ratios. The table below is a simplified summary aid in judging the helpfulness of a diagnostic test given a likelihood ratio.[16]

Usefulness of Likelihood Ratios

Usefulness	**Likelihood Ratio (+)**	**Likelihood Ratio (-)**
Conclusive	>10	<0.1
Moderately Helpful	5-10	0.1-0.2
Possibly Helpful	2-5	0.5-0.2
Not Helpful	1-2	0.5-1

This table shows that the further away a likelihood ratio is from 1.0, the more helpful it is in determining the diagnosis. Since this is derived from the sensitivity and specificity, the higher the percentage values of sensitivity and specificity, the better the likelihood ratios and the more helpful the test will be.

EVALUATING EFFICACY OF THERAPY

There are several ways to express the effectiveness of a treatment.

The *absolute risk reduction* (ARR) describes the "risk change": risk of the control patients minus the risk of the treatment patients ($R_C - R_T$)

The *relative risk reduction* (RRR) is calculated as follows: risk change divided by original risk [$(R_C - R_T)/R_C$]

The *relative risk* (RR) equals the "new risk" divided by the "original risk" (R_T/R_C)

As a hypothetical example, let's assume that a randomized clinical trial has been conducted on an eye drop to treat dry eye symptoms. The study reveals that 45% of the control group had dry eye symptoms and 20% of the treatment group had dry eye symptoms. The ARR is (45%-20%=) 25%. The RRR is (25%/45%=) 55%. The RR is (20%/45%=) 0.44. Translated into "plain language", these calculations show that using the eye drop changed (reduced) the risk of dry eye symptoms by 25%. It also says that the percentage of the treatment group with symptoms is 55% lower than the percentage of the control group with symptoms. Finally, the relative risk data suggests that the treatment group has about four-tenths of the risk of having dry eye symptoms compared to the control group.

Note that the RR is a "percentage of a percentage" and will always make the beneficial effects of a treatment look better versus the ARR.[7] For example, in the Ocular Hypertension Treatment Study, the incidence of glaucoma in the treated group was 4.4% after 5 years, versus 9.5% in the untreated group. The RRR is 0.54 (implying a risk reduction of 54%). The ARR, however, was 5.1%. Both convey an impression of risk reduction, but the difference in the numbers is ten-fold.[17]

The numbers in the hypothetical example give the doctor and patient a rough idea of the benefit of a treatment ("large benefit" or "small benefit" or "no benefit"), but the calculated values may seem too mathematical or abstract. Other calculations can be derived from the risk calculations to provide a different view of the study in more practical terms. Foremost of these calculations (and popularized by the evidence-based movement) is the *number needed to treat* (NNT). The NNT is simply 100/ARR (since ARR is expressed as a percentage). In the example above, the NNT would be equal to 4. (NNT values are always rounded up to the nearest integer since NNT relates to number of patients.) An NNT of 4 implies that a doctor needs to treat 4 patients before significantly helping 1 patient. One must be careful in interpreting NNT. For conditions which are less common in the population, the NNT can be skewed to a high value because the incidence rate in the control group is directly accounted for in the calculation.[17] Such high values for NNT can discourage clinicians from pursuing treatment even though the only reason why the NNT is high is because the disease is very rare. Also, if the patient population in a clinical study has a greater severity of disease compared to the population-at-large, the ARR could be very impressive. But, if the treatment is approved and marketed for use by less severely affected patients, the ARR would be much smaller.[18]

Relative risk is applicable to cohort studies and randomized clinical trials. When analyzing retrospective case-control studies, or for uncommon events, the *odds ratio* is analogous to relative risk but not equivalent.[11, 19] This is because prospective and retrospective studies differ in how the data are derived. In randomized trials, patients are designated as treated or not treated (or "exposure" versus "no exposure"); then, the proportion with the outcome is determined in each group. In case-control studies, relative risk cannot be calculated because the patients are selected with the outcomes (instead of initially being assigned to exposure/no-exposure groups). So, an "incidence" cannot be calculated. Because case-control studies are not randomized, they are unable to address temporal or causal relationships.[11] Odds ratio is an indirect estimate of the strength of association between outcome and whether or not the patients were exposed. Comparisons of formulae for relative risk versus odds ratio will be discussed below.

ESTIMATING PROGNOSIS

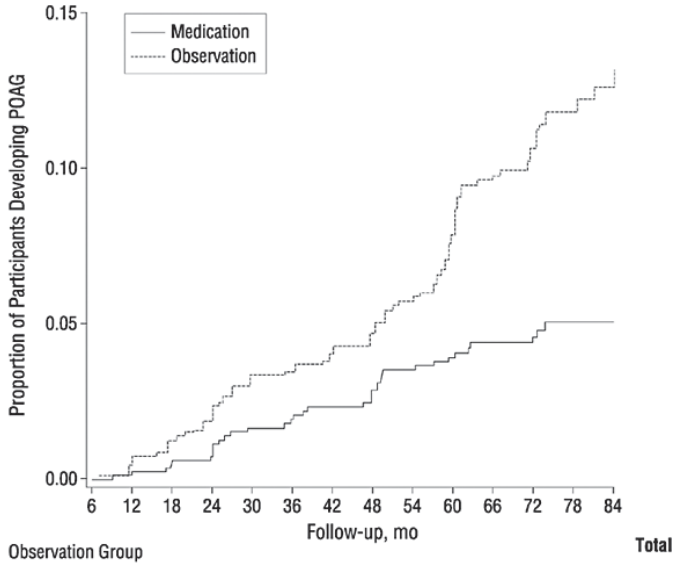
Assuming a patient has been administered a reliable diagnostic test, a diagnosis can either be ruled in or ruled out. If a patient has been reliably labeled with a diagnosis, the question naturally asked next is "what are the chances the disease will progress" to some feared outcome (e.g., blindness, death, etc.)?

Prognosis for any given condition is usually expressed in one of three ways in the published literature: as a percentage of survival at a particular point in time (for example, a 5-year survival rate); as median survival (the length of time in which half of the study patients have not survived); or as survival curves that depict the percentage of patients which have not yet reached the adverse endpoint (for example, death).[4] A common type of survival curve appearing in the literature is the Kaplan-Meier survival curve which plots percentage of survival on the y-axis versus time on the x-axis. When

the term "survival" is used in everyday discourse, the term is taken to mean "not dying." "Survival" in the realm of prognosis can be used to apply to outcomes other than death, however (e.g., "not going blind, "not having a heart attack", etc.).

Data on prognosis is helpful in counseling patients on whether or not to initiate treatment, or giving guidance as to when treatment should be initiated. Having knowledge of median survival time or knowing the "shape" of the survival curve can help a patient and doctor weigh the expected benefit of treatment at a particular time after diagnosis versus any risks inherent in the treatment.

Figure 1. Example of a Kaplan-Meir plot. This is figure 4 from "The Ocular Hypertension Treatment Study: A Randomized Trial Determines That Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open-Angle Glaucoma" by Michael A. Kass, MD; Dale K. Heuer, MD; Eve J. Higginbotham, MD; Chris A. Johnson, PhD; John L. Keltner, MD; J. Philip Miller, AB; Richard K. Parrish II, MD; M. Roy Wilson, MD; Mae O. Gordon, PhD; for the Ocular Hypertension Treatment Study Group. *Arch Ophthalmol.* 2002;120:701-713. Available at: http://archopht.ama-assn.org/cgi/content/full/120/6/701 and used to direct the reader to Archives of Ophthalmology. "Optometric Care within the Public Health Community" is not a commercial publication.



Observation Group															Total
At Risk	819	809	800	789	772	753	742	721	696	673	601	506	357	204	
POAG	1	5	6	10	5	3	4	9	4	24	3	9	1	5	**89**
Deaths	0	1	1	4	3	2	4	4	3	2	1	0	2	2	**29**
Inactive	9	3	4	3	11	6	13	12	12	10	4	2	0	0	**89**

Medication Group															
At Risk	817	797	787	775	759	751	739	731	708	690	648	536	372	210	
POAG	0	2	3	7	1	5	0	9	1	5	0	3	0	0	**36**
Deaths	2	2	5	3	1	0	2	3	1	0	3	2	1	1	**26**
Inactive	18	6	4	6	6	7	6	11	10	4	4	2	0	0	**84**

Kaplan-Meier plot of the cumulative probability of developing primary open-angle glaucoma (POAG) by randomization group. The number of participants at risk are those who had not developed POAG at the beginning of each 6-month period. The number of participants classified as developing POAG is given for each interval. Participants who did not develop POAG and withdrew before the end of the study or who died are censored from the interval of their last completed visit.

EVALUATING THE POTENTIAL FOR HARM

Primum non nocere: "first, do no harm." The goal of health care is to help and not harm, but practically every medical intervention – diagnostic or therapeutic – carries some level of harm along with its benefit. Diagnostic tests can pose harm particularly if the tests are invasive in nature. Treatments can be harmful toxicologically (for example, use of a medication) or physically harmful to the body (for example, radiation or lasers). In fact, as many as half of all new drugs have at least one harmful side effect which was unknown at the time the drug was approved.[11] Harm can also arise from the environment and not be directly related to receiving treatment (for example, the increased risk of lung cancer from smoking).

In the Treatment discussion above, the relationship between ARR and NNT was presented. An analogous relationship exists with respect to harm. Risk can increase with treatment and an *absolute risk increase* (ARI) can be calculated (risk of the treatment patients minus the risk of the control patients ($R_T - R_C$). The *number needed to harm* (NNH) is calculated as 100/ARI. As an example, there is some controversy about the use of a particular therapy (biphosphonate) for treating postmenopausal osteoporosis. Studies have shown that this particular drug can be used for 5 years without posing significant risks. However, it is thought that using the drug for more than 5 years could lead to microfractures of bones and other adverse effects. Using the drug for 10 years resulted in an ARI of fracture of the vertebrae of 2.9%. The NNH (that is, the number of women who would need to be treated for the longer treatment period to result in 1 additional fracture) is 100/2.9 = 34.[20]

INCORPORATING A PATIENT'S VALUES AND PREFERENCES

One criticism of the plethora of statistical tests associated with EBM is that a patient's view of the risks and benefits do not receive a deserved level of attention amidst the calculations. One way in which to account for a patient's preferences is, ironically, to use yet another mathematical formula for *likelihood of being helped and harmed* (LHH)=(1/NNT):(1/NNH).[4] Translated, this ratio can give a patient a feel for the likelihood of being helped versus being harmed by the therapy in question. For example, if a particular drug had an ARR of 5% (the NNT equals 20) and an ARI of 0.2% (the NNH equals 500), the LHH=(1/20):(1/500) =25. Risk-averse patients might feel that a particular value of LHH is too low to consider the treatment, whereas more risk-taking personalities might view this treatment as "worth the gamble."

CONFRONTING BIAS IN CLINICAL RESEARCH

Human nature can interfere with the cold mathematical objectivity of a study of a treatment or diagnosis.. By happenstance or with deliberation, clinical trials can be unduly influenced by acts or omissions of study coordinators. The results of research can be tainted and unreliable with the bias introduced by study design. There are many types of bias which can be introduced into clinical research, including:[7]

Filter bias – patients who are enrolled in studies are usually there because they have a health concern; otherwise they never would have gone to the doctor and heard about

the clinical trial in the first place. Some patients get filtered out while others have a higher tendency toward needing/wanting a test or treatment by virtue of having a health characteristic that matches the needs of a clinical trial.

Review bias (also context bias) – interpretation of a test can be affected by the results of other tests or presence of signs of symptoms. For example, a radiologist is more likely to diagnose pneumonia on an x-ray if they are told the patient has signs or symptoms of pneumonia (such as cough or fever).

Publication bias – Studies which show statistically significant results are more likely to be published than those that show no benefit for the treatment or test in question. If looking at the whole body of literature for a given exposure, and most of the publications show positive results, one may be tempted to believe the results are overwhelming, when in fact if all of the studies -- published and non-published – were evaluated the results may be far less spectacular.

Recall bias – Retrospective studies which rely upon patients' memories about certain exposures may show that case patients will be more likely than controls to recall that they were exposed.

Recruitment bias – People who volunteer for clinical trials tend to have a higher-than-average socioeconomic status and level of education.[21]

A loss of patients in a clinical trial can lead to spurious conclusions and readers of articles must be careful to note whether or not a sufficient number of patients who enrolled in a clinical trial remain at the conclusion of the trial. If a patient has dropped out of a trial, the question needs to be asked, "Why?" Did the patient die or have some other serious morbidity (either by random chance or due to the exposure being tested in the trial)? Was the patient lost to follow-up (due to poor recordkeeping by the researchers)? Did a patient refuse further treatment because of complications or ineffectiveness of the assigned treatment? A clinical study is considered complete when all participants have been accounted. Patients who drop out should be included in any data analysis for the group to which they were originally assigned. This is called *intention-to-treat analysis*. If patient data are removed from a trial for reasons associated with treatment (death or complication), this introduces a source of bias.[7] For example, if an experimental drug causes a side effect not experienced in the control group, subjects in the experimental group may have a higher drop out rate. If the outcome showed improvement in those who completed the trial, but did not account for the high drop out rate, a falsely high improvement would be reported. Intent to treat analysis includes the data from-drop outs up to the time of drop out and classifies them accordingly. Thus, treatment effect is reported for all patients who start treatment. This reflects clinical practice where some patients are lost to follow up. Reader should apply the "5-and-20 rule" to account for intention-to-treat. If less than 5% of the study's participants are lost to follow-up, then such loss has minimal impact on the outcome of the study. If more than 20% of the patients are lost to follow-up, the reader should be very wary of the validity of the study as a whole. If the drop-out rate is between 5 and 20 percent, caution should be exercised in trusting the study's results, and the article's

author should be prepared to provide information on the impact of attrition on the study's results.[22]

One must also examine carefully the protocols of clinical studies to see if they reveal any favoritism toward one therapy over another.[11] For example, a clinical trial compared two eye drops for treating glaucoma: timolol and latanoprost. Standard treatment with timolol requires it be used every 12 hours. Its maximum reduction in intraocular pressure occurs 1 to 2 hours after administration and wears off rapidly. Latanoprost lasts much longer with maximum reduction in intraocular pressure about 8 to 12 hours after administration. Because of the differences in duration, comparative intraocular pressure measurements should be performed several times during the day. This particular study took one measurement immediately *before* one of the doses of timolol, so that timolol's effect was likely completely worn off whereas there was likely a good amount of effect remaining from the latanoprost. The measurements of intraocular pressure were stacked in favor of latanaprost.[23]

Published reports of clinical trials will include a "methods" section which summarizes how research was conducted and protocols used by the researchers. Characteristics important for interpreting clinical trials are not always made available within published studies or *are not accounted for in weighing the evidence* (for example, ethnicity). If there are ambiguities which need to be clarified, one place to look is at the actual protocols. Many protocols of clinical trials, particularly those involving serious health conditions, are registered and available for viewing at "ClinicalTrials.gov".[11] It is also common for researchers or research groups to have their own web pages, either at their university web site or independently. They often post more details on methods and results then are published.

COMPARING ONE JOURNAL TO ANOTHER

The explosion of the "information age", ready access to computers and the pressure in academia to publish in peer-reviewed periodicals has created an overwhelming array of journals (an estimated 20,000 medical journals[11]) and journal articles from which to sift in search of that "pearl" of wisdom in helping a patient. As of the end of 2008, typing the word "eye" in the Pubmed search box yields 552,837 "hits" in the database. If the search is limited to randomized clinical trials, the number of hits is still 9,360. Where does one begin to weed out the "good" source journals from the "not so good"?

Many different criteria have been used to evaluate journals within a particular field of healthcare, including: frequency of use of the journal, opinions or checklists, inclusion in databases of medical and scientific literature, and bibliometric statistics.[24]

Perhaps the evaluation method receiving the most attention is the impact factor. A journal's impact factor describes the rate of citation of papers from that particular journal. The average citation rate of all of the articles from a journal is the means to calculate the journal impact factor. This factor in turn can be used to rank the "quality" of the research appearing in a journal. Journals will cite a high impact factor in their advertising to attract more readers.[25] There are limitations and potential flaws in using a crude number such as citation rate of a journal's articles. For example, articles in basic

science journals typically only reference basic science journals, but clinical science journals often cite references originating from basic science as well as clinical science journals. This gives the basic science journals an upper hand in terms of impact factor.[24] In emerging fields of science or medicine, the number of journals is relatively few, but interest in the topic may be disproportionately large compared to more "mundane" fields of study. This can lend to a higher impact factor for the new field due to a small denominator (few articles) and a large numerator (a lot of citations of these articles on the "ground floor" of new technology).[25] It is for these reasons and others that journal impact factor can be a first step toward finding research helpful to evidence-based analysis, but should be used with caution.

Can Healthcare Professionals Be (Successfully) Trained in Evidence-Based Medicine?

The compelling reason to engage in evidence-based research is to improve the well-being of patients. If the data is there, can a healthcare professional be taught how to sift through the evidence to determine a proper course of patient management?

Numerous publications demonstrate the ability to train professionals in EBM principles and for the trainees to retain the information, whether the training is provided online or in the lecture hall. [26-28] Some components of EBM were retained more readily than others,[26] and disappointingly, one study showed that despite intensive training, one-fourth of doctors were still unable to proceed past the first step of evidence-based practice (ie, formulating an appropriate clinical question to research for their patient's case).[29] Other researchers observed similar inability to form clinical questions and also poor ability to search for relevant articles necessary to make clinical decisions.[30]

Once professionals are trained to retrieve evidence, interest in using electronic sources of information can fade quickly. As the novelty wears off, or if the system is not readily accessible or "user-friendly", the enthusiasm to perform research of the evidence base diminishes. Clinicians who felt that pursuit of the evidence had resulted in improved patient care were the ones who tended to continue using the databases over the long term.[31]

Demonstrating the preponderance of evidence favoring a particular diagnostic test, treatment or prognostic factor is not always sufficient motivation to get healthcare providers to do the act accordingly. Many factors can influence the final decision made on patient management. Patient's fears or preferences or beliefs, insurance coverage, government policies and pharmaceutical marketing can steer patient care away from the evidence in a different direction.

Evidence-based studies can temporarily influence patterns of practice, but external forces can make those changes short-lived. As an example, the treatment of hypertension was unsettled by a large clinical trial in 2002 which challenged the benefits of newer versus older drugs. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) study concluded that diuretics, which are inexpensive and longstanding medications for hypertension, were superior in many ways to newer and more expensive classes of hypertensive medications.[32] Almost immediately after

the study was published, physicians shifted toward prescribing diuretics. [33] Despite efforts by the National Institutes of Health to broadcast the evidence-based results of the ALLHAT study, growth in the use of diuretics was not sustained and the number of diuretic prescriptions declined. Observers blame the lack of growth on marketing by competitors of diuretic medications which paid speakers to interpret the ALLHAT results "in ways that made their products look better."[34] Although diuretics have side effects as any drugs do,[35] it was concerning that the main results of a land mark clinical trial did not affect prescribing patterns as much as expected.

Efforts have been made to incentivize evidence-based medicine in continuing education. In 2005, the American Academy of Family Physicians began offering double credit to physicians attending approved continuing education courses that incorporate evidence-based medicine into the lecture.[36] Evidence-based presenters were twice as likely to use evidence-based websites and journal articles to prepare their presentation versus the non-approved lectures. Presenters of non-approved lectures were twice as likely as the evidence-based presenters to rely upon their "own experiences", anecdotes and textbooks for course content. Attendees felt evidence-based medicine was important to improving the quality of meetings, but they rated the evidence-based courses as equal in quality to the non-approved lectures.

A higher level of care can be delivered in both small and large offices when evidence-based medicine is fully integrated into clinical decision making .[37] Support and enthusiasm from the leaders in the department, along with access to the evidence-based literature, training in answering a focused question, and collaboration with other disciplines and organizations, are successful strategies to make evidence-based medicine the norm.[38] Changing practice patterns from "the way it's always been done" in favor of embracing evidence-based medicine is aided by self-evaluation and creating positive intentions to redesign the way one delivers care.[39]

Weighed against the scientific data are the beliefs, concerns and fears of patients and doctors alike. Patients' values and perceptions of quality-of-life may preclude them from heeding the evidence in favor of other treatments or tests. Questions of quality-of-life may lead a patient to decline chemotherapy for cancer; fears of complications may deter patients from electing surgeries or other therapies; concerns about cost or financial burden may force a patient to use a generic medication rather than a more efficacious brand name, or forego compliant use of medication altogether. By the same token, fear by doctors of being sued for malpractice might compel them to order lab tests even when the evidence concludes it is unnecessary.[40]

The Presence of Evidence-Based Practice in Eye Care

As primary healthcare providers within a specialty, optometrists hold a unique responsibility in not only having to be familiar with the evidence base in eye care, but also being prepared to employ evidence on systemic conditions as well.[41]

Several published resources are available which review the evidence of common eye disorders.[10, 41] There are at least 110 periodicals devoted to optometry, ophthalmology

and vision science.[42] The body of evidential knowledge in eye care (as in other specialties) is constantly growing and evolving, as reflected by the hundreds of articles that are subsequently cited thousands of times in subsequent articles.[24] Not all of these articles are evidence-based. One study of a year's worth of articles appearing in a prominent ophthalmology journal showed that less than 15 percent of articles pertaining to treatment were assessed as having strong evidence. The lack of evidence was attributable largely to lack of randomization of treatment groups.[43] Although the number is alarmingly low, the 15 percent figure does not fare poorly compared to other disciplines (for example, 20 percent of anesthesiology articles employed randomized clinical trials).[44]

Examples of Evidence-Based Eye Care

From the cornea to the visual cortex, evidence-based medicine can play a role in all facets of eye care. The following are examples of clinical questions that have benefited from the application of evidence-based medicine. A variety of eye conditions and types of studies (with different rankings of quality of evidence) are presented here to serve as an introduction to the potential benefits of evidence-based medicine.

Comparison of techniques in the diagnosis of Acanthamoeba *keratitis*[1]*. Acanthamoeba* is a genus of ameobae which is waterborne and can cause sight-threatening infections of the cornea. If diagnosed promptly, appropriate treatment can be applied to preserve vision. In a retrospective cohort study, patients with "atypical" keratitis were identified for analysis. Patients in this cohort had scrapings of the cornea performed and cultures were grown to look for the presence of Acanthamoeba. These same patients also received a test called confocal microscopy which viewed the cornea with a particular type of microscope that can produce images of extremely high magnification to detect the presence of ameobic cysts. In the study, scraping and culture tests in various forms were assigned the role of "gold standard" by which to compare the validity of confocal microscopy. In one set of data, the sensitivity of confocal microscopy was 90.9% and the specificity was 90.1%. The likelihood ratio was 9.2. The authors conclude that confocal microscopy is a useful adjunct to culture in diagnosing *Acanthamoeba* keratitis. Its ease of use and quick results compared to incubation of a culture make it a favorable tool for rapid diagnosis.

Preventing side effects of anesthesia during pediatric strabimus surgery. Two frequent and major complications during strabismus surgery are the oculocardiac reflex and vomiting. The oculocardiac reflex is a physiological response to physical stimulation of the eye or structures surrounding the eye. The result of the reflex is a cardiac arrhythmia attributable to stimulation of the heart via the trigeminal nerve.[45] Although extremely rare, the fairly common oculocardiac reflex is capable of causing cardiac arrest.[46] Postoperative vomiting can cause complications in wound healing as well as

[1] Tu EY, Joslin CE, Sugar J, Booton GC, Shoff ME, Fuerst PA. The relative value of confocal microscopy and superficial corneal scrapings in the diagnosis of anacthamoeba keratitis. Cornea 2008 27(7):764-72.

dehydration. Up to half of school-aged children will experience post-operative vomiting after anesthesia.[47] A prospective randomized clinical trial was performed to determine whether particular anesthetics and antiemetic agents would reduce the risk of either oculocardiac reflex or vomiting.[48] Four different combinations of medications were administered for anesthesia and to prevent vomiting (for the sake of simplicity, the categories will simply be called Exposures *A, B, C* and *D*). When patients from Exposure A were compared to those of Exposure B, the incidence of vomiting 6 hours after surgery decreased from 26% to 8%. (The absolute rate reduction was 26%-8%=18%). The number needed to treat is 5. Patients in Exposure C were given an agent which decreased vomiting, but was suspected of increasing the risk of oculocardiac reflex. Patients in Exposure D were not given the anti-vomiting agent. This study showed no benefit with the antiemetic agent, but more noteworthy was an increase in oculocardiac reflex with Exposure C (40% incidence) compared to Exposure D (14% incidence). (The absolute rate increase in ocularcardiac reflex was 40%-14%=26%). The number need to harm was 4. The researchers concluded that vomiting can be controlled by isoflurane versus propofol , but the specific antiemetic drug used in the study not only proved insignificant in preventing vomiting, it increased the risk of oculocardiac reflex.

Risk of cataract formation with use of intranasal corticosteroids. The risk of cataract formation with use of steroids has been well-established since the 1960's.[49] Use of intranasal corticosteroids for the treatment of allergic rhinitis has been linked with cataract formation. A retrospective observational cohort study of the incidence of cataract among users of oral and intranasal steroids was performed in the United Kingdom using a database of 286,000 patients.[50] The patients were separated into 3 groups: (1) subjects exposed to intranasal corticosteroids only, (2) subjects exposed to oral corticosteroids only, and (3) subjects not exposed to any corticosteroids. The incidence of cataract in each group was determined by searching the database for specific cataract diagnosis codes. Cases were each matched to 4 control patients. The relative risk of cataracts in intranasal steroid users was calculated to be 1.0 (the confidence interval was 0.8-1.2). The relative risk in oral steroid users was calculated to be 2.1 (the confidence interval was 1.8-2.5). The researchers concluded that intranasal corticosteroid use was not associated with cataract formation.

Prognosis in patients being treated for glaucoma. A randomized prospective clinical trial (the Early Manifest Glaucoma Treatment Study [EMGT][51,52]) was performed to track the progression of glaucoma over a 4-year period. The treatment group received laser trabeculoplasty and was placed on a beta-blocker eye drop. The control group received no treatment. Patients were examined every 3 months in search of any signs of glaucoma progression. This included worsening of the peripheral visual field and increased cupping of the optic disc. At 4 years, the progression of glaucoma was reduced by approximately 50% with treatment. The median survival for the control group was about 3.5 years. The trial, at the 4-year mark, demonstrated clear benefit for having treatment to lower the intraocular pressure in preventing progression of glaucoma.[51] The EMGT also serves as an example of a trial continuing to reap evidence. The EMGT is now providing data from patients being followed for as long as

11 years, further solidifying the conclusions of the first publications of the trial as well as shedding light on newer theories on progression of glaucoma.[52]

Age-related macular degeneration and the influence of diet. It is theorized that ARM is a result of oxidative damage to the retina, and that dietary antioxidants can help prevent the progression of ARM. A randomized controlled trial, the Age-Related Eye Disease Study (AREDS), examined the role of antioxidants in delaying progression in patients with intermediate levels of ARM.[53] Compared with a placebo group, the group which received antioxidants had statistically significantly reduced odds of developing advanced staged ARM (odds ratio of 0.72). Another group of researchers performed a meta-analysis to determine whether antioxidants (9 different ones examined in the collection of studies) can prevent the progression of ARM from the early stage to the intermediate stage. 12 studies met the inclusion criteria – all were prospective studies (but only 3 were randomized control trials).[54] The odds ratios pooled from the studies for each of the 9 antioxidants showed no significant benefit for taking antioxidants in preventing early stages of ARM. The authors concluded that there is no basis for recommending the use of antioxidants in preventing ARM.

Convergence insufficency and treatment of symptoms. Convergence insufficiency is a common binocular vision disorder characterized by difficulty in converging the eyes or eye discomfort with convergence. A randomized, placebo controlled trial was performed to determine which of several treatments would be effective in helping patients with convergence insufficiency.[55] Patients in the treatment group were allocated to one of 4 interventions -- 2 were office-based eye exercise regimens (with home reinforcement) and 2 were home-based. The treatment duration was for 12 weeks. The most intense of the office-based therapies produced significantly improved symptoms compared to the other 3 therapy groups. 73% of the intense office-based treatment patients had improved outcomes, but only about 1/3 of the home-based treatment patients showed improvement. The 2 home-based therapies were no better than placebo. Although patients undergoing office-based treatment had higher compliance, this alone did not statistically explain the better results with office-based treatment.

Meta-analysis of outcomes of cataract surgery. A meta-analysis was performed to determine whether the length of waiting time for cataract surgery has an effect on patient outcomes.[56] This analysis identified 27 studies that met criteria for further analysis. Being able to pool the results of all of these studies led the researchers to draw several conclusions: patients who waited less than 6 weeks for cataract surgery experienced better visual acuity and quality-of-life outcomes than those who waited 6 months or longer. Patients who waited longer for surgery were at higher risk for experiencing multiple falls (and fractures). Overall patient satisfaction decreased as waiting times increased.

One eye or two? The presence of a pathological condition in one eye does not necessarily imply that the pathology exists in the other eye. So, the question becomes: can (or should) a clinical trial use data from one eye or both eyes of a single patient? There are advantages and disadvantages to using both eyes for studying conditions

such as glaucoma. Using both eyes essentially doubles the number of data points and therefore reduces variability in measurement. Disadvantages include loss of predictive accuracy from information unique to each eye and from any relevant data comparing one eye against the other eye.[57] A report on predicting glaucoma compared the accuracy of prediction using data from three groups of data: values from both eyes, values from both eyes along with the absolute difference between eyes for eye-specific variables, and data from the one eye at higher risk of developing glaucoma. The report concluded that all 3 models of data analysis were in high agreement with each other in predicting development of glaucoma. Use of values from both eyes was recommended over the other two groups because it was the simplest to use and had the least variability in measurements.[57] Not all eye diseases or conditions are expected to occur in both eyes simultaneously, and using data from both eyes would be counterintuitive. However, using data from both eyes does strengthen the evidence in some cases.

Use of Risk Calculators in Eye Care

Attempts to increase applicability and to tailor treatment to individual patients has prompted development of tools such as risk calculators. Risk calculators are nomograms, tables or software programs which assist doctors in calculating parameters relating to harm or prognosis. Given an individual patient's data (for example, intraocular pressure, age, smoking status, etc.), the calculator can generate a profile of risk for developing the disease or complication in question. One example of a risk calculator for glaucoma is accessible at http://ohts.wustl.edu/risk/calculator.html. When patient data is input, a value is presented of the percentage risk of developing glaucoma within 5 years. This particular calculator allows for actual values to be entered (eg, 63 years of age), or use of a simpler tool that utilizes a point system with categorical data (for example, age 55 to <65, in lieu of the exact age of 63). There is also a fee-based calculator available online for calculating risk of macular degeneration at http://www.sightrisk.com/calculatingrisk.asp. For calculating evidence-based statistics in general (for example, NNT, ARR, likelihood ratio, odds ratio, etc.), there are online calculators, such as the Evidence Based Calculator accessible at http://moosenose.com/EBCalculator.htm.

Evidence-Based Public Health

Traditional evidence-based medicine has been directed at providing individual clinicians reliable information for treating one patient at a time. Is there a role for evidence-based practice in addressing the needs of larger populations or communities? The public health literature has begun to embrace the principles of evidence-based healthcare to guide policymakers and public health practitioners in determining what measures should be taken for the public good.

Whereas evidence-based medicine seeks out the most solid research in the form of randomized clinical trials, evidence-based policy relies upon careful testing of various policy and program options.[58] Typical evidence-based care makes the "unit" of care recipient the individual patient, whereas in public health interventions the unit of care recipient is a neighborhood or community. Performing well designed observational

cohort studies at the level of the neighborhood or city is difficult and expensive.[59] Those that have been done, such as the Framingham studies, provide a wealth of good quality information. Randomized clinical trials are often impossible or unethical to conduct in some areas of public health.[60, 61] Because of these differences in clinical care versus public health, the core competencies of evidence-based public health differ from evidence-based medicine. In addition to evaluating levels/quality of evidence, an evaluator of evidence-based public health must be able to assess the suitability of the intervention (therapy, screening, health policy or regulation) as well as judge the population outcome based on social criteria such as equity, cost-effectiveness, acceptability, and applicability across subgroups in the population.[6]

The use of systematic reviews in public health is increasing and a large number of them examine public health laws (for example, laws on blood alcohol content and their effect on drunk-driving deaths).[62]

Just as evidence-based medicine in the clinic can be influenced by factors such as patient fears and concerns, evidence-based health policy decisions can be clouded by the miasma of lawmaking. Hindrances to "good governance" can include the emotional power of anecdotes from constituents, conflicting information or viewpoints disseminated by the media, jurisdictional conflicts as well as lobbying efforts by special interest groups. A prime example of the effects of these impediments is the persistent concern over the correlation between vaccinations and autism. The evidence-based literature does not show a link between thimerasol-containing vaccines and the development of autism in children,[63] yet the debate remains unresolved.[64] As one observer notes, "A politically relevant study can be more marketable than a high quality study."[65]

Factors as seemingly esoteric as elective term-limits may also hinder informed policymaking as institutional knowledge and "memory" of the cumulative health care evidence is lost.[61] Furthermore, because policymaking can offer a host of interventional choices (eg, regulation, tax incentives or surtaxes, criminal penalties, or education), choosing the appropriate policy to test (and committing resources to it) can be challenging. There are so many variables involved in implementing a policy or regulation that one must acknowledge that it can be a complex process. The decisions must be based on the evidence and the specific context in which the process is performed.[58] Reliance upon experts from other fields, such as geography, sociology, anthropology, and information technology can help better understand the context and streamline the process of managing the evidence.[66]

The evidence base does serve as a stimulus to action in health policymaking. When public concern about a health problem exceeds public opposition, the chances of implementing a policy to address the health concern become more likely.[6] Aspects such as cost-effectiveness can drive decisions to fund programs. Cost-benefit studies can compel lawmakers to impose limits, such as tobacco control to prevent disease as well as lower the costs of health insurance premiums. Just as health professionals can be taught the principles of evidence-based research, policymakers, lawmakers and administrators also can be taught how to sift through the literature and ferret out the

evidence to combat the falsehoods and hearsay cited by parties interested in the policy question at hand.[61]

Many public health activities at the community level center around health promotion and education. The impact of community-based health promotion has been largely characterized as only modest. The inability to generate marked improvements in health through these programs may be attributable to several possible reasons. It might stem from a fundamental failure to agree on the objectives of health education. Some health educators believe that increasing knowledge is an adequate ends to implementing health education campaigns while others emphasize the objective to change behavior. Other factors to consider are the inability to control societal trends that affect both control and intervention groups, limits to depth and width of intervention to influence community behavior, and power struggles over control of promotion programs between researchers and participating community leaders.[59] Once "the word gets out" about a potentially beneficial health behavior, members across all communities may adjust their behaviors, whether or not they were part of the control or intervention group in a study. A situation such as this is akin to being unable to blind all of the subjects to the treatment in a clinical trial. This can diminish the difference in outcomes between control and intervention groups.

Practice Guidelines

Central to the proposed health care reforms in the U.S. is the use of evidence-based research to make decisions on clinical effectiveness and cost effectiveness.[67] Moving care toward effectiveness and application of effectiveness in providing care may depend upon practice guidelines to assist clinicians in making decisions about the most appropriate care. Clinical practice guidelines are templates for clinicians to follow from diagnosis to treatment in an evidence based manner accepted by the medical community. Clinical practice guidelines may rely heavily on systematic reviews and other high-ranking types of evidence-based medical research. An example of a platform to disperse guidelines to clinicians on a broad level (eg, nationally accepted practice guidelines) is the type of system in the *Map of Medicine* proprietary software package which is available online at www.mapofmedicine.com. Adherence to guidelines is enhanced if the practice recommendations are non-controversial, clearly stated, do not require a change in existing practice routines and are evidence-based.[6] Caution must be exercised to avoid conflicts of interest in the development of clinical guidelines. Authors of guidelines have been known to have intimate financial ties with pharmaceutical manufacturers – entanglements which only saw the light of day after the issue was publicly questioned.[68]

Success of clinical guidelines has been limited by the culture of healthcare as well as flaws in the process of developing guidelines. Doctors embrace a right to autonomy in making decisions for their patients and a "rigid" guideline or algorithms with forced choices run counter to that autonomy. Since they are also "merely" guidelines, they are viewed as voluntary.[38] The definition of whether a treatment works can vary from study to study. Another problem is that guideline developers do not always distinguish between the "possibility" and the "probability" that a patient will benefit.[68] Once a

treatment has demonstrated efficacy and has been approved for clinical use, one could presume that "anything is possible" – there is a high possibility that some benefit will arise from its use. However, the probability that an actual health benefit is observed could be very low. For example, a drug could have a high possibility of lowering the intraocular pressure by one or two points, but the probability that the patient's eye health actually benefits from this lowering of pressure could be extremely low.

From a policy point-of-view, the next logical step from practice guidelines will be the funding or reimbursement of care based upon adherence to practice guidelines and the evidence base. Government policy centers have used systematic reviews since the late 1990's in decisions regarding coverage of certain ailments. Medical directors of health plans have used systematic reviews as a basis of whether or not to cover controversial or experimental therapies.[14] Decisions about whether or not to cover standard therapies are also being held to the standards of good evidence. For example, the State of Washington mandates that the "best available scientific and medical evidence" should guide coverage decisions by state government agencies that purchase health care. Consortia, such as the Drug Effectiveness Review Panel – a collaboration of governmental and non-governmental organizations – examine the evidence on safety and efficacy of various drugs, and make recommendations about which drug in each drug class is expected to be the all around best drug to use for a given diagnosis.[69]

While many developed countries are accustomed to the use of evidence-based principles in caring for patients and developing health policy, inequalities exist internationally in the ability to employ evidence-based public health. International researchers have commented on the inability to access databases which contain the evidence, a paucity of data originating within their country's health care system (data which may be reflective of their value systems, culture and most pressing health priorities), as well as the inability to apply the evidence from more developed countries due to lack of resources.[3, 70] Efforts are being made to develop databases of evidence that have greater relevance to the international community.[70]

CASE STUDY: Pandemic Influenza

Avian flu (H5N1) began infecting birds in the late 1990s. Isolated human infections were soon reported. If a mutation occurs, Avian flu may develop a means for human to human transmission. As a new flu virus, it has the potential to cause pandemic. Swine flu (H1N1) had not been active in a known population since the end of the 1918 pandemic. In 2008, an outbreak occurred in Mexico and quickly spread to the U.S. and other countries. How can public health professionals act to minimize the effects of pandemic flu?

As mentioned previously, the traditional randomized control trial is not always available for evidence-based public health. In the case of pandemic influenza, such a situation holds true and a literature review led some researchers to utilize alternative types of evidence to develop community-wide recommendations for preventing the spread of influenza during a pandemic. A systematic review of the literature for non-pharmaceutical (not involving vaccines or drugs) interventions to prevent spread of

influenza was undertaken and the review yielded very little in terms of high-quality research (e.g., randomized trials). The authors then convened a meeting of experts to poll their opinions on the efficacy of a variety of strategies to prevent the spread of influenza during a pandemic.[71] Thirteen experts from a broad range of disciplines relating to pandemic influenza were asked to identify possible non-pharmaceutical interventions. This list was then culled down to 56 items, which each expert rated as important or not important in different phases of a pandemic. The results of the survey showed wide support for measures such as hand washing but not for such strategies as use of masks by the general public. Voluntary measures versus government mandates were more often recommended by the experts. This study highlights the lack of scientific evidence to drive public health policy and also identifies the need for education, persuasion and social support to develop actual policies to implement recommendations.

Epistemological Assumptions and the Ethics of Evidence-Based Medicine

A number of criticisms have been leveled against evidence-based medicine in regards to its philosophical underpinnings as well as it actual practice and application. The first group broadly consists of questions regarding the assumptions of science truth-seeking and knowledge, of how we *know* what we *claim* to know – what is generally referred to as epistemology and more precisely as the "philosophy of science." The second group of criticisms is aimed, perhaps more pragmatically, at the particular ways in which scientific/medical investigators conduct their research and then seek to apply their predominantly statistical findings to individual patients in the clinical setting.[72]

What constitutes *good* evidence is central to evidence-based medicine, yet there are few randomized, controlled trials demonstrating that evidence-based medicine itself results in superior patient outcomes.[73] As Dr. John Service points out, we must "take on faith" that knowledge generated by evidence-based medicine is superior to other ways of knowing: "The failure to conduct a randomized control trial, the recognized best form of evidence according to EBM, and reliance on expert opinion, namely theirs (the worst form of evidence according to them), hoist EBM by its own pretard."[74] This kind of epistemological paradox is not unique to EBM, but it does underscore one of its pivotal and foundational assumptions.

Moreover, the practice of science requires operational assumptions about previously adjudicated "truths," including the non-signficance of an entire universe of (recognized and unrecognized) independent variables,[75] the lack of effect of observation on outcomes (an assumption long since vanquished from quantum physics given the Heisenberg Uncertainty Principle[76]), and political/non-rational influences on scientific discourse and agreement such as those postulated by Polanyi,[77] Kuhn,[78] and Foucault.[79] Some have even questioned the very notion of physical causality altogether.[80]

Like all science, EBM relies on testing hypotheses that are created within the previously established framework and assumptions of what Kuhn calls "normal science," observation of outcomes wherein the investigator/clinician/observer interacts with

subjects/patients/outcomes with the potential for unintended and/or under-appreciated consequences, and may be subject to at least some non-rational influences (including unproven assumptions about the nature of "good evidence" and the conflation of statistical association with causation). Accordingly, EBM is subject to the same sorts of criticisms leveled more generally by contrarian philosophers of science.[81]

Related to but distinct from such epistemological criticisms of EBM are those focused on its methods and practical applications. A number of critics have noted that EBM discounts historical wisdom and clinical experience.[82-84] J.W. Fairley's observation is typical:

> *"The refusal to give due weight to accumulated professional wisdom is a peculiarly Western scientific version of historical nihilism, and an unattractive quality of EBM. The advice to "*burn your traditional textbooks*" belittles the efforts and achievements of our predecessors…This assumption of professional ignorance forms the fundamental basis for applying RCT's in all areas of medicine."*[85]

Though proponents of EBM counter that its implementation is a multi-stepped process that includes integration of clinical expertise and patient values with the "best available external clinical evidence from systematic research,"[19, 86] its hierarchical ordering of evidence clearly supports the notion that statistical data generated by meta-analysis of randomized, controlled clinical trials is superior to ancestral wisdom and practitioner experience. There is an air of both a historical conceit and definitional circularity associated with EBM and its teaching;[87] proponents appear to define EBM vacuously as whatever approach to medicine answers the question "how ought we to practice medicine?"[72]

Other common methodological criticisms directed at EBM include its reductionism (that outcomes derived from analysis of populations do not necessarily apply to individual patients, particularly those in under-studied populations),[82] publication bias (against contrarian findings and inclusion within meta-analyses),[88] diminution of basic science,[87] limited generalizability of RCT's with increasing complexity of patient populations or in circumstances where randomization is patently unethical (e.g., coronary bypass surgery),[89] exclusion of non-medical approaches to disease and disability[90]and, more broadly, a structural emphasis on research questions that serve the interests and values of powerful groups, including the professions and health care organizations:[91] "What passes for objective research is a search for what elites want knowledge about."[92] As Straus and McAlister contend, however, at least some of these difficulties are "limitations universal to the practice of medicine" and, as such, are not unique to evidence-based medicine or evidence-based practice.[19]

Ethics of Evidence-Based Public Health

Broad-based interventions, such as those in health policy, run the risk of threatening the autonomy of the individual citizen, and in some cases, the autonomy of certain levels of government (municipal, state, and arguably even a nation's right to self-govern).

Ordinances or regulations which impinge upon an individual's right to engage in an activity may be viewed as paternalistic. For example, when laws were first being drafted for mandatory use of seat belts in automobiles, it was argued that the potential harm to one person – in spite of the number of lives it could save – was a paternalistic decision which threatened the autonomy of the individual. Policymakers are taken to task to demonstrate not only safety but efficacy in the proposed law in the context of the value systems of society and acceptable thresholds of imposition on rights of the individual.[6]

Each level of government may feel similar paternalistic encroachment by jurisdictions above them. Cities may feel encroached upon by health policies (which are typically viewed as one of the "state's rights issues") and states may feel powerless in light of federal decisions (for example, funding issues for Medicaid or air pollution control laws). Nations may be in an analogous position when other nations apply pressure in affairs such as nuclear non-proliferation or exportation of goods which enter the food supply chain and other products that can carry potential harm.

Take Home Conclusions

Evidence-based medicine employs statistical tools and defined protocols to bring uniformity to study design and analysis. Once "apples" can be compared to "apples", the quality of the information hopefully becomes more reliable. Course of treatments should be more predictable for better informed consent and healthier outcomes.

- The most important step in researching a condition is to determine the right question to research.
- Randomized controlled clinical trials are the gold standard for quantifying health care diagnosis and treatment, but other study designs (cohort, case-control) can provide good quality results.
- Evidence Based Medicine can be taught to practitioners but recidivism is common.
- Relative risk, adjusted relative risk, number needed to treat, number needed to harm are important results from studies which can be easily explained to patients to assist their decision making process.
- Practitioners should employ a defendable method in acquiring information, evaluating research, and applying it to individual patients.

Study Questions

1. Write a focused clinical question for the following patient scenarios:
    a. A patient with high myopia, best corrected visual acuity of 20/30 each eye, mild cataracts, and desires surgery so she does not have to wear glasses.
    b. A six year old with anisometropic amblyopia (20/100) wants the best treatment.
    c. A 64 year old white male, whose mother is legally blind from macular degeneration wants to do everything possible to prevent macular degeneration. Exam reveals RPE mottling but no drusen.
2. List the hierarchy for quality of study designs.
3. What is publication bias?
4. What are some limitations of EBM in public health research?
5. Do you feel the criticisms of EBM are justified?

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