

The Medical Literature

Users' Guides to the Medical Literature

VIII. How to Use Clinical Practice Guidelines

A. Are the Recommendations Valid?

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CLINICAL SCENARIO

You are relieved to find that the last patient in your busy primary care clinic is a previously well 48-year-old woman with acute dysuria. There has been no polydipsia, fever, or hematuria; the physical examination reveals suprapubic tenderness; and urinalysis shows pyuria but no casts. You arrange cultures and antibiotic treatment for a lower urinary tract infection. On her way out the door, your patient observes that her friend has just started taking "female hormones," and she wonders whether she should too. Her menstrual periods stopped 6 months ago and she has never had cervical, ovarian, uterine, breast, or

cardiovascular problems, but her mother had a mastectomy at age 57 for postmenopausal breast cancer. You give the same general advice you have offered similar patients in the past, but suggest that the matter be discussed at greater length when she returns after completing the antibiotic treatment. Later, as you lament doorknob consults, you are irritated when a colleague asserts that your primary advice about prophylactic hormone replacement therapy (HRT) was wrong and that you should have recommended exactly the opposite. You resolve to revisit this disagreement, armed with the best evidence.

THE SEARCH

You begin by using Grateful Med to look for a recent overview because many articles about prophylactic HRT have appeared recently, your time is short, and your patient would want to know about all significant benefits and harms associated with HRT. On the first subject line of the Grateful Med search, you select "estrogen replacement therapy" by marking this as a major concept in the list of Medical Subject Headings (MeSH) that Grateful Med associates with the term "estrogen." After limiting your search to English-language reviews (Publication Type="review"), you still have 131 articles to consider. A quick scan of the first 25 titles reveals diverse topics, including the effect of HRT on lipid profiles, bone density, fracture

rates, and the incidence of endometrial, cervical, and breast cancer. Knowing that "practice guideline" is among the publication types listed by Grateful Med, you reason that clinical practice guidelines might address multiple HRT-related outcomes at one time, and thus provide you with the most efficient access to the best summary or summaries of the available data. A repeat search with the new publication type yields five citations. Two of these are "technical bulletins" of the American College of Obstetricians and Gynecologists,^{1,2} one is written for surgeons,³ one is a recent guideline from the American College of Physicians (ACP),⁴ and the last is a commentary on the ACP guideline.⁵ Observing that the ACP guideline is published together with a systematic overview of the evidence supporting its recommendations,⁶ you begin your review of issues in HRT decision making with the ACP guideline.

INTRODUCTION

Clinicians serve patients by addressing each individual's health care needs. This includes recognizing important health problems, considering sensible options for managing each problem, interpreting evidence about the outcomes of each option, and ascertaining patient

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Users' Guides to the Medical Literature section editor: Drummond Rennie, MD, Deputy Editor (West), JAMA.

Are the recommendations valid?**Primary guides:**

Were all important options and outcomes clearly specified?

Was an explicit and sensible process used to identify, select, and combine evidence?

Secondary guides:

Was an explicit and sensible process used to consider the relative value of different outcomes?

Is the guideline likely to account for important recent developments?

Has the guideline been subject to peer review and testing?

What are the recommendations?

Are practical, clinically important, recommendations made?

How strong are the recommendations?

What is the impact of uncertainty associated with the evidence and values used in the guidelines?

Will the recommendations help you in caring for your patients?

Is the primary objective of the guideline consistent with your objective?

Are the recommendations applicable to your patients?

preferences for each outcome. Increasingly, clinicians must also consider the resource implications of their decisions. This involves detecting, treating, palliating, and preventing health problems in a way that maximizes the public good achieved with available resources.

To meet patients' expectations, individually and in aggregate, clinicians face intimidating tasks of information management. Overviews can help by systematically gathering, selecting, and combining evidence that links options to outcomes. Clinical decision analyses can help by refining questions and exploring the trade-offs between competing benefits and harms. Economic analyses can help by tallying the costs associated with different options. While useful, these approaches do not always synthesize information in a way that directly supports specific clinical recommendations.

Clinical practice guidelines, which have been defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances,"⁷ represent an attempt to distill a large body of medical knowledge into a convenient, readily usable format.⁸ Like overviews, they gather, appraise, and combine evidence. Guidelines, however, go beyond most overviews in attempting to address all the issues relevant to a clinical decision and all the values that might sway a clinical recommendation. Like decision analyses, guidelines refine clinical questions and balance trade-offs. Guidelines differ from decision analyses in relying more on qualitative reasoning and in emphasizing a particular clinical context.

Guidelines make explicit recommendations, often on behalf of health organizations, with a definite intent to influence what clinicians do. These suggestions about what should be done go beyond a simple presentation of evidence, costs, or decision models. They reflect value judgments about the relative importance of various health and economic outcomes in specific clinical situations. As a result, they should be required to pass unique tests about how matters of opinion, in addition to matters of science, are handled.

When appraising a consultant's counsel, we are impressed if she states and explains her suggestions clearly, discusses alternatives, and acknowledges possible biases and extenuating circumstances. We can use this common-sense approach to assess the validity, importance, and applicability of clinical practice guidelines. In this article, we offer suggestions for deciding whether to use a clinical practice guideline in formulat-

ing one's own clinical policies (Table). Our focus is on evaluation of interventions—including prevention, diagnosis, and therapy—that are designed to improve important patient outcomes. For prevention and diagnosis, this involves looking beyond the accuracy of the test to the ultimate consequences of choosing a diagnostic strategy on patients' morbidity, mortality, and health-related quality of life.

We use the same basic questions as the users' guides for original research articles, overviews, and decision analyses. Are the recommendations valid? If they are, what are the recommendations and will they be helpful in patient care? To answer these questions, we draw on an emerging literature about practice guideline development and evaluation⁹⁻¹⁵ (and S. H. Woolf, unpublished data, 1991), while emphasizing the perspective of practitioners who must adopt, adapt, or reject recommendations. Busy clinicians might hope that criteria for appraising practice guidelines would obviate the need for reviewing how the guideline developers have brought together the evidence, and how they have chosen the values reflected in their recommendations. Unfortunately, any shortcuts that bypass at least a cursory look at evidence and values will leave the clinician open to being misled by guidelines that may be based on a biased selection of evidence, a skewed interpretation of that evidence, or an idiosyncratic set of values. Shortcuts that do not highlight health conditions and interventions, patients and practitioners, and benefits and harms will leave the clinician open to misapplication of guidelines in clinical practice.

ARE THE RECOMMENDATIONS VALID?

Primary Guides

You need to determine whether guideline developers used appropriate methods and adduced evidence that support

the recommendations made. If developers do not include—either in their policy statement or in a supporting article—information about how they chose options and outcomes, selected evidence, and decided on values, you might suspect that these steps were not done systematically.¹⁶ In any case, you cannot evaluate such guidelines, and their recommendations probably should not influence your decision making.

Were All Important Options and Outcomes Considered?—Guidelines pertain to decisions and decisions involve choices and consequences. To appreciate why a particular practice is recommended, you should check to see that guideline developers have considered all reasonable practice options and all important potential outcomes.

Whether developers present guidelines for prevention, diagnosis, therapy, or rehabilitation, they should specify both the interventions of interest and sensible alternative practices. For example, in a guideline based on a careful systematic literature review,¹⁷ the ACP offers recommendations about medical interventions for preventing strokes.¹⁸ While carotid endarterectomy is mentioned as a possible surgical intervention in the preamble to the guideline, the procedure is not considered in the recommendations themselves. This guideline could have been strengthened if medical interventions for transient ischemic attacks had been placed in a management context that included the highly effective surgical procedure.¹⁹

In its HRT guideline, the ACP makes recommendations about counseling women who are postmenopausal and are considering HRT to prevent disease and prolong life.⁴ The interventions they considered were (1) long-term daily prophylaxis (10 to 20 years) with 0.625 mg of oral conjugated estrogen, (2) daily estrogen and medroxyprogesterone acetate (2.5 mg orally per day or 5 to 10 mg on days 10 to 14 of the month), (3) short-term HRT therapy (1 to 5 years), or (4)

no prophylactic hormone use. The guideline did not consider calcium supplementation, newer estrogen delivery systems, or other approaches to the prevention of osteoporosis-related fractures.

Guideline developers must consider not only all the best management options, but all the important consequences of the options. As a clinician looking after individual patients, you look for information on morbidity, mortality, and quality of life and you must decide if the guideline ignores outcomes that your patients would care about. As a practitioner interested in using resources efficiently, you must also mind economic outcomes. Whether developers examine economic outcomes at all—and if they do, whether they look at costs from the patients', insurers', or health care system perspective, or consider broader issues such as the consequences of time lost from work—can strongly influence final recommendations.²⁰ The majority of published guidelines do not include formal cost analyses, those that do use a variety of analytic techniques, and it will be difficult for you to determine whether actual cost estimates are valid or applicable for your practice setting. You can gain a better understanding of the potential importance of these issues by seeing if the economic projections are subjected to sensitivity analysis. If so, you can gauge the extent to which guideline recommendations might change if assumptions about costs change. You can also check to see if the guideline developers offer clinically relevant comparisons. For example, the average cost of preventing one cardiovascular-related death by means of HRT might be compared with the cost of doing the same by means of cholesterol reduction, blood pressure control, or smoking cessation counseling.

In its HRT guideline, the ACP used lifetime probability of developing endometrial cancer, breast cancer, hip fracture, coronary heart disease, and stroke, and median life expectancy to estimate risks and benefits for subgroups of women. They acknowledged possible HRT effects on serum lipoproteins, uterine bleeding, sexual and urinary function, and the need for endometrial surveillance by biopsy, but did not include these considerations in the model used to synthesize evidence. The effects of HRT on costs and quality of life, which could have a major impact on patient choices, were not explicitly considered.

Was an Explicit and Sensible Process Used to Identify, Select, and Combine Evidence?—Having specified options and outcomes, the next task in decision making is to estimate the likelihood that each outcome will occur. In effect, one has a series of specific ques-

tions. For HRT, what is the effect of the alternative approaches on hip fracture incidence, on myocardial infarction and coronary death, or on breast and endometrial cancer incidence? Guideline developers must bring together all the relevant evidence, and then combine that evidence in an appropriate manner. In carrying out this task, they must avoid bias that will distort the results. In effect, they must have access to, or conduct, a systematic overview of the evidence bearing on each question they address.

The users' guide on overviews includes criteria that can be used to judge whether guideline developers have done an adequate job in accumulating and synthesizing evidence.²¹ Developers should specify a focused question, define appropriate evidence using explicit inclusion and exclusion criteria, conduct a comprehensive search, and examine the validity of the results in a reproducible fashion.

The best guidelines define admissible evidence, report how it was selected and combined, make key data available for your review, and report that they found randomized trials that link the interventions to the outcomes. Such randomized trials may, however, be unavailable, and guideline developers are in a different position from the authors of overviews who may abandon their project if there are not any high-quality studies to summarize. Many important clinical problems are technically, economically, or ethically difficult to address with randomized clinical trials. Because guideline developers must deal with inadequate evidence, they may have to consider a variety of studies as well as reports of expert and consumer experience. They must formulate recommendations, but they should be candid about the type and quantity of evidence on which those recommendations are based.

The nature and appropriate use of expertise is one of the most hotly debated areas in guideline development. Sometimes "experts" have preeminent knowledge of the basic science, pathophysiology, and natural history of a health condition. They may also be distinguished by extensive direct clinical experience. Persons who have witnessed and understood the limitations of clinical trials in the clinical domain offer another dimension of expertise. For some guidelines, extra emphasis may be placed on the expertise of generalists who can gauge the practical implications of interventions applied to large groups. Although the RAND Corporation and others have developed protocols for recording and quantifying expert assessments

of the appropriateness of health interventions,^{22,23} guideline developers must decide what type of expert opinion to solicit and how to incorporate it into the evidential foundation for guideline development. You are unlikely to find systematic methods for selecting, capturing, and grading relevant expertise in today's guidelines, but you should try to determine whether and how expert opinion was used to fill in gaps in the evidence from clinical trials.

A quality-of-evidence scale can be used to rate different categories of evidence (eg, expert opinion or clinical investigation) and methods for producing it (eg, blinded or nonblinded outcome assessment) according to the likelihood that the source or design will yield biased results.²⁴ Developers working on a different problem with a different supporting literature may devise an evidence-filtering instrument that stratifies case-control studies into categories of differing quality.²⁵ The prospective development and application of a systematic approach to appraising and classifying evidence is important because this means that the strength of the evidence in support of the recommendations can be reported. Strategies for summarizing the strength of both evidence and recommendations will be addressed in the second of our articles about using practice guidelines, which deals with interpreting and applying the results.

The ACP HRT guideline developers searched MEDLINE (1970 to 1991) and citations from articles, and conferred with expert consultants to identify studies published in English about the treatment options and outcomes. They conducted formal overviews, including meta-analysis, and derived summary estimates of relative risks and lifetime probabilities of the principal outcomes with and without HRT for subgroups of women. These subgroups included women without risk factors; women at increased risk for coronary disease, hip fracture, or breast cancer; and women who had a hysterectomy. Their overviews met the validity criteria we have suggested. In most cases, randomized trials had not been conducted, and the investigators relied on observational studies. Therefore, they appropriately conducted sensitivity analyses to determine the implications if the results of observational studies represented overestimates or underestimates of the true effect of the interventions on the relevant outcomes.

Secondary Guides

Was an Explicit and Sensible Process Used to Consider the Relative Value of Different Outcomes?—Link-

ing treatment options to outcomes is largely a question of fact and a matter of science. In contrast, assigning preferences to outcomes is largely a question of opinion and a matter of value. The extent to which HRT increases the incidence of breast cancer or decreases death rates from myocardial infarction can be ascertained from the evidence. The relative importance placed on avoiding breast cancer or cardiovascular disease depends on what patients care about most. Consequently, it is important that guideline developers report the sources of their value judgments and the method by which consensus was sought.

You should look for information about who was *explicitly* involved in assigning values to outcomes, or who, by influencing recommendations, was *implicitly* involved in assigning values. Expert panels and consensus groups are often used to determine what a guideline will say. You need to know who the panel members are, bearing in mind that panels dominated by members of specialty groups may be subject to intellectual, territorial, and even financial biases (some organizations screen potential panel members for conflicts of interest, others do not). By identifying the agencies that have sponsored and funded guideline development, you can decide whether their interests or delegates are overrepresented on the consensus committee. Panels that include a balance of research methodologists, practicing generalists and specialists, and public representatives are more likely to have considered diverse views in their deliberations.

Even with broad representation, the actual process of deliberation can influence recommendations. You should therefore look for a report of methods used to synthesize preferences from multiple sources. Informal and unstructured processes for arbitrating values may be vulnerable to undue influence by individual panel members, particularly the panel chair. Appropriate structured processes increase the likelihood that all important values are duly considered.²⁶

It is particularly important to know how patient preferences were considered. Health interventions have beneficial and harmful effects along with associated costs, and recommendations may differ depending on our relative emphasis on specific benefits, harms, and costs. What is the relative importance of an uncertain risk for increases in breast cancer vs a fairly clear expectation of decreased incidence of heart attacks and strokes? Many guideline reports, by their silence on the matter of patient preferences, assume that guideline developers adequately represent pa-

tients' interests. Methods for directly assessing patient and societal values exist but are rarely used by guideline developers. You may be limited to gauging whether the values implicit in the guideline appear to favor patient, third-party (eg, reimbursement agencies), or societal priorities.²⁷ You can also consider which ethical principles—such as patient autonomy (the patient's control over decisions about her health), non-maleficence (avoiding harm), or distributive justice (the fair distribution of health care resources)—prevailed in guiding decisions about the value of alternative interventions. For guidelines based on formal risk-benefit and cost-benefit analyses, declarations of acceptable levels of risks and costs per benefit achieved can help you make comparisons across guidelines.

Variation (disagreement) and uncertainty (ambivalence) in values could affect summary recommendations and so should be recorded and reported by guideline developers. The clinical problems for which practice guidelines are most needed often involve complex trade-offs between competing benefits, harms, and costs, usually under conditions of uncertainty. Even in the presence of strong *evidence* from randomized clinical trials, the effect size of an intervention may be marginal or the intervention may be associated with costs, discomforts, or impracticalities that lead to disagreement or ambivalence among guideline developers about what to *recommend*. Explicit strategies for documenting, describing, and dealing with dissent among judges, or frank reports of the degree of consensus attained, can help you decide whether to adopt or adapt recommendations. Unfortunately, until guideline development methods mature, you will rarely find this information.

An example of the implicit, and perhaps questionable, value judgments guideline developers make comes from the ACP recommendations for medical therapies to prevent stroke.¹⁷ This guideline recommended that aspirin be considered the drug of choice in patients with transient ischemic attacks, and suggested that ticlopidine be reserved for patients who do not tolerate aspirin. The best estimate of the effect of ticlopidine relative to aspirin in patients with transient ischemic attacks is a 15% reduction in relative risk, a benefit that would translate into preventing one stroke for every 70 patients treated in a group of patients with a 10% risk of stroke. The ACP presumably makes their recommendation that aspirin, not ticlopidine, be the drug of choice for patients with transient ischemic attack on the basis of

the increased cost of ticlopidine, and the need for checking the white blood cell count in patients receiving ticlopidine. This implicit value judgment could be questioned, and the guideline would be strengthened if the authors had made the values that underlie their judgment explicit.

In the case of the ACP HRT guideline, the developers gave priority to outcomes that are major contributors to morbidity and mortality in North America (eg, the effect of long-term estrogen use on risk of death from myocardial infarction, osteoporosis-related fractures, and endometrial cancer), but acknowledged that other considerations may be as important as preventing disease and death for some women (eg, resumption of menses, changes in mood, and sexual function). The task of assigning relative value to different types of morbidity or causes of mortality is left to patients and their clinicians.

Is the Guideline Likely to Account for Important Recent Developments?—Guidelines often concern controversial health problems about which new knowledge is actively sought in ongoing studies. Because of the time required to assemble and review evidence and achieve consensus about recommendations, the guideline may be out of date by the time you see it. You should look for two important dates: the publication date of the most recent evidence considered and the date on which the final recommendations were made. Some authorities also identify important studies in progress and new information that could change the guideline. Ideally, these considerations may be used to qualify guidelines as "temporary" or "provisional," to specify dates for expiration or review, or to identify key research priorities. For most guidelines, however, you must scan the bibliography to get an impression of how current a particular guideline may be. The ACP HRT guideline gives dates for evidence considered (1970 through 1991) and final approval (March 1992). The guideline acknowledged that its advice about use of estrogen in combination with a progestin was limited by uncertainty about whether the progestin neutralizes the beneficial effects of estrogen on risk factors for unwanted cardiovascular outcomes. The guideline did not alert readers to watch for results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, initiated in 1988, which would directly address that uncertainty. An early report from the PEPI group concludes that estrogen alone or in combination with a progestin improves lipoprotein levels and lowers fibrinogen levels without detectable effects on insulin or blood pressure.²⁸

Has the Guideline Been Subjected to Peer Review and Testing?—People may interpret evidence differently and their values may differ, and guidelines are subject to both sorts of differences. Your confidence in the validity of a guideline increases if external reviewers have judged the conclusions reasonable, and clinicians have found the guidelines applicable in practice. If the guidelines differ from those adduced by others, you should look for an explanation. On the other hand, if the guidelines meet the first four validity criteria and the underlying evidence is strong, rejection by clinicians or peer reviewers may have more to do with their biases than to any limitation in the validity of the guidelines.

If the underlying evidence is weak, no matter what the degree of consensus or peer review, the clinicians' confidence in the validity of the guideline will be limited. In the second part of our users' guide for practice guidelines, we will describe explicit frameworks for judging the strength of recommendations.

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The weaker the underlying evidence, the greater the argument for actually testing the guideline to determine whether its application improves patient outcomes.²⁹ The question for any such test would be: are patient outcomes better, or are outcomes equivalent at decreased cost, when clinicians operate on the basis of the practice guidelines?

Weingarten and colleagues³⁰ conducted such an investigation examining the impact of implementation of a practice guideline suggesting that low-risk patients admitted to coronary care units should receive early discharge.³⁰ On alternate months over the period of a year, clinicians either received or did not receive a reminder of the guideline recommendations. During the months in which the intervention was in effect, hospital stay for coronary care unit patients was approximately a day shorter and the average cost of the stay was over \$1000 less. Mortality and health status at 1 month were similar in the two groups. The investigators concluded that the guideline reminder reduced hos-

pital stay and associated costs without adversely affecting measured patient outcomes. Although in this case the authors used alternate-month allocation, which makes the study weaker than a true randomized trial, a study of this type helps to validate the predicted consequences of guideline implementation for defined outcomes.

Once you are confident that the clinical practice guideline addresses your clinical question and is based on a rigorous up-to-date assessment of the relevant evidence, you can review the recommendations to determine how useful they will be in your practice. While not pristine, the ACP guidelines on HRT do a good job at meeting the primary criteria for using a practice guideline. We will describe how to interpret and apply the results in the next article of this series.

We offer special thanks to Deborah Maddock who has provided outstanding administrative support and coordination for the activities of the Evidence-Based Medicine Working Group.

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