

Evidence-based care: 2. Setting guidelines: How should we manage this problem?

Evidence-Based Care Resource Group

There are four steps in determining how to manage a clinical problem. The first is to formulate questions that are answerable; the second is to locate and synthesize the evidence needed to answer the questions; the third is to estimate the expected benefits, harms and costs of each option based on the evidence; and the fourth is to judge the relative value of the expected outcomes to conclude whether the benefits are worth the harms and costs. It is impractical to repeat these steps for every clinical decision. Therefore, implicitly or explicitly, physicians rely on guidelines, "rules" that simplify decision making about complex problems. If the methods used to develop a guideline are not explicit it is difficult or impossible to know how much confidence to place in it. Therefore, for common and important clinical problems, physicians should rely on guidelines that are systematically developed using explicit methods.

Il y a quatre étapes à suivre pour décider comment traiter un problème clinique. Il faut d'abord formuler des questions auxquelles il est possible de répondre, ensuite, trouver et résumer les données nécessaires à cette fin, troisièmement, évaluer les avantages, les préjudices et les coûts prévus de chaque solution possible en fonction des données et, enfin, établir la valeur relative des résultats attendus afin de déterminer si les avantages valent les préjudices et les coûts en jeu. Ces étapes ne sont pas pratiques dans le cas de chaque décision clinique à prendre. C'est pourquoi les médecins comptent implicitement ou explicitement sur des lignes directrices, des «règles» qui simplifient la prise de décisions au sujet de problèmes complexes. Si les méthodes d'élaboration d'une ligne directrice ne sont pas claires, il est difficile ou impossible de savoir dans quelle mesure il faut s'y fier. C'est pourquoi, dans le cas des problèmes cliniques communs et importants, les médecins devraient compter sur des lignes directrices élaborées de façon systématique à l'aide de méthodes explicites.

Should you treat a 75-year-old woman with a systolic blood pressure of 180 mm Hg? Should you refer a 65-year-old man with symptomatic, benign hypertrophy of the prostate for surgery? What should you tell a woman of 55 who wants to know whether she should start hormone replacement therapy? How should you manage a case of acute myocardial infarction in a 45-year-old man? Should you order a glucose tolerance test for a 35-year-old woman who is in her 26th week of pregnancy? Should you refer a 25-year-old man with

Members: Drs. Andrew D. Oxman (chair and principal coauthor), David A. Davis, John W. Feightner (principal coauthor), Neil V. Finnie and Brian G. Hutchison, Ms. Sandy Lusk and Drs. Peter J. MacDonald, Ron G. McAuley and John W. Sellors

Drs. Oxman, Feightner, Hutchison, McAuley and Sellors are in the departments of Family Medicine and of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ont. Drs. Davis, Finnie and MacDonald and Ms. Lusk are in the Department of Family Medicine, McMaster University. Dr. Oxman was the recipient of a Career Scientist Award from the Ontario Ministry of Health.

Reprint requests to: Evidence-Based Care Resource Group, Department of Family Medicine, Rm. 2V6, Health Sciences Centre, McMaster University, 1200 Main St. W, Hamilton, ON L8N 3Z5; fax (905) 528-5337

This article is the second in a series of five that began in the Apr. 15, 1994, issue of CMAJ.

acute low-back pain for spinal manipulation? What should you recommend to a sexually active girl of 15? How should you manage acute otitis media in a child of 5?

Clinicians are confronted daily with decisions such as these. They must decide which questions to ask patients, what to include in a physical examination, which diagnostic tests to order, what to tell patients, which interventions to recommend or use and what follow-up is needed. To aid in making these decisions physicians, implicitly or explicitly, must rely on guidelines — simple decision rules for resolving complex problems.^{1,2}

For example, a decision on whether to treat systolic hypertension in elderly patients entails four key steps (Fig. 1). First, an answerable question must be posed. Second, the evidence needed to answer the question

must be located and critically reviewed. Third, the expected benefits (e.g., reduced risk of stroke), harms (e.g., side effects of drugs) and costs of treatment must be estimated. Finally, a judgement about the relative value of the expected benefits, harms and costs must be made. If the treatment of 100 patients for 5 years prevents 3 of them having a stroke, 1 having a heart attack and 2 or 3 suffering congestive heart failure yet will result in 3 or 4 patients having intolerable side effects,³ is systolic blood pressure in elderly patients worth treating?

It is impractical and unreasonable to analyse clinical decisions, especially common ones, repeatedly this way. Instead, physicians rely on guidelines such as: "Hypertension therapy should be prescribed for patients 60 years of age and older with isolated systolic hypertension (diastolic blood pressure less than 90 mm Hg and

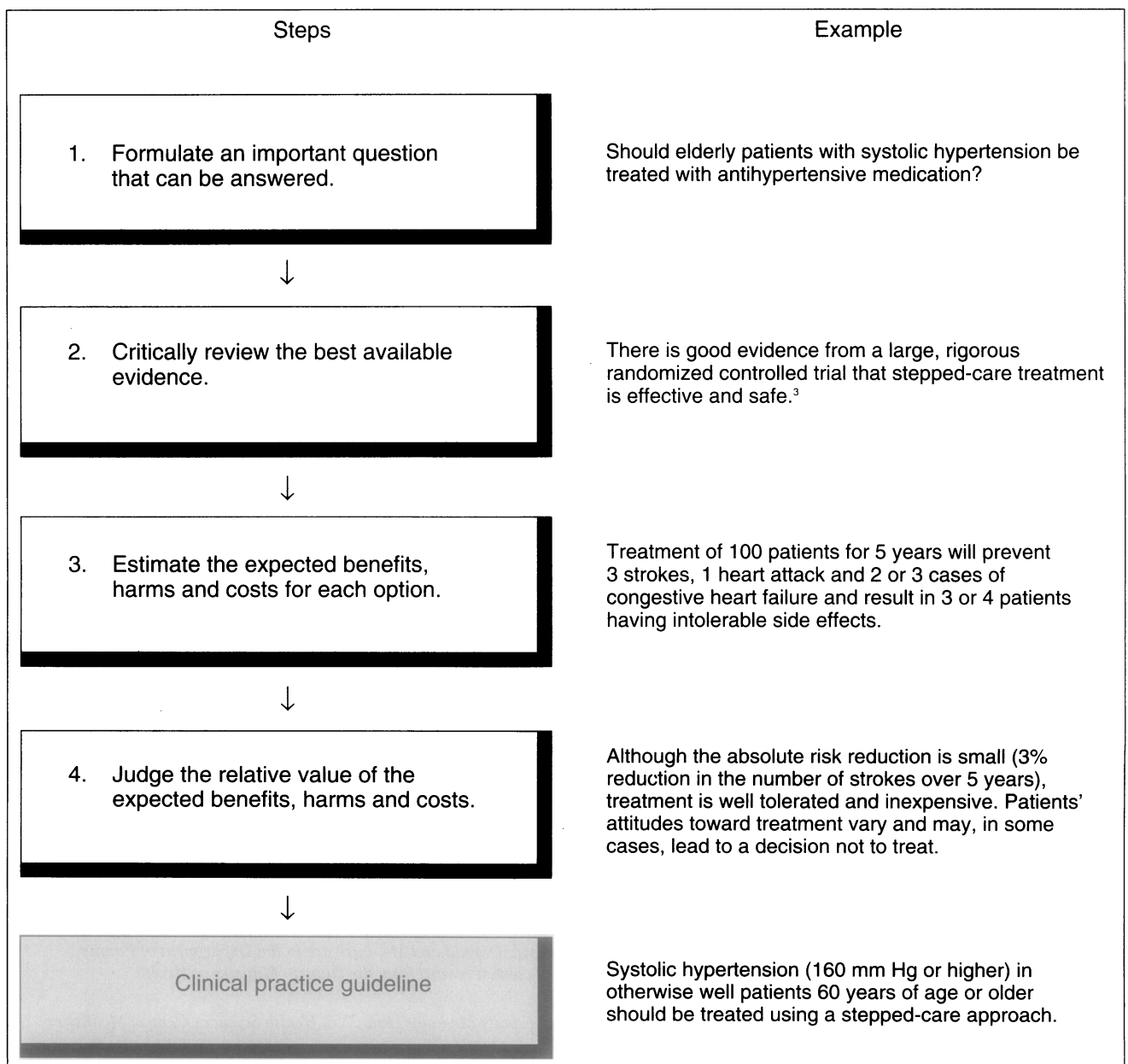


Fig. 1: Key steps in developing a clinical practice guideline.

systolic blood pressure 160 mm Hg or higher).^{7,4} With the use of such a guideline a complex problem becomes manageable.

Of course, the quality of the care depends on the quality of the guidelines used. In this article we will outline some important considerations in each of the four key steps in determining appropriate guidelines for clinical practice.

These considerations also apply to guidelines developed with an implicit approach or nonsystematically;⁵ however, the considerations shown in Fig. 1 should be addressed systematically to avoid potential mistakes that occur in nonsystematically derived guidelines,^{6,7} and methods for setting guidelines should be explicit to enable critical appraisal of the guidelines' validity.⁸

What is the problem?

After deciding that a problem is important⁹ physicians should characterize the patients to whom the decisions apply and clarify the options and outcomes of interest. In the first article of this series we identified two types of problems: how to manage a clinical condition and how to improve the delivery of health services. In both cases a decision must be made. There are always at least two options (e.g., to use or not to use an intervention) and often several. There is at least one outcome of interest, and typically there are several, including potential benefits, harms and costs. Examples of the target patients, options and outcomes for various clinical problems are shown in Table 1. The next three steps become

clearer after the problem has been specified in this way.

What is the evidence?

Occasionally the benefits of an intervention are so clear, and the harms and costs so small, that there is little or no need for rigorous evaluation (e.g., transfusion for massive blood loss, injection of epinephrine for anaphylaxis, administration of penicillin for pneumococcal pneumonia and reduction of a dislocated elbow in a toddler). The effectiveness of most care is not so obvious, and rigorous evaluations are needed to determine whether the perceived benefits are real and worth while.

To ensure that good research is translated into good clinical decisions clinicians must be informed consumers.¹⁰ A large amount of medical information is not supported by valid research, including some articles published in prestigious medical journals and recommendations made by leading authorities.^{11,12} Clinicians must be selective about what they read and heed to ensure that it is applicable and valid. The opinion of authorities and one's own clinical experience are not adequate to validate the results of research.¹²⁻¹⁴ To make informed decisions clinicians must be informed users of medical research and have the ability to appraise it critically.¹⁵

This does not mean that each clinician must review all of the original research relevant to his or her practice. For much, if not most, of what clinicians do they have to rely on others to locate, critically appraise and synthesize the research in the form of a systematic review^{16,17} or practice guidelines.⁷

Table 1: Examples of target patients, options and outcomes for various clinical problems

| Problem | Target patients | Option | Outcomes |
|--------------------------|---|---|---|
| Therapy | Patients with acute asthma | Oral corticosteroid therapy | Benefit: Improved functional status Harm: Side effects Costs: Cost of drugs, savings from reduced hospital use |
| Prevention | Patients who have had a myocardial infarction | ASA* prophylaxis | Benefit: Reduced risk of cardiovascular (CV) events Harm: Side effects Costs: Costs of drugs and side effects, savings from CV events prevented |
| Diagnosis | Adult patients with sore throat | Throat swab of mucous sample for culture | Benefits: Increase in indicated treatment with penicillin, reduction in unnecessary treatment and side effects Harm: Delay in starting indicated treatment and relieving symptoms Costs: Costs of culture and treatment |
| Screening | Asymptomatic adult patients | Screening for total serum cholesterol level | Benefit: Reduced risk of CV events Harms: Adverse consequences of follow-up, labelling Costs: Cost of test and follow-up, savings from CV events prevented |
| Health services delivery | Patients seen in primary care practice | Computerized reminders for periodic health examinations | Benefit: Improved delivery of effective preventive services Harm: Deterioration in delivery of services for which reminders are not provided Costs: Cost of computerization, time spent contacting patients and performing examinations |

*ASA = acetylsalicylic acid.

Criteria for screening articles about therapy, prevention, diagnostic tests and health service studies, review articles and clinical practice guidelines are summarized in Table 2. If an article has met these criteria it is more likely to be valid.

In some areas, such as general internal medicine,¹⁹ obstetrics²⁰ and neonatology,²¹ there are information sources that have already applied similar criteria. The *ACP Journal Club* prepares structured summaries of articles on general internal medicine selected from more than 40 journals that meet validity criteria like those in Table 2.¹⁹ Similar efforts have been started or are planned for other disciplines (Dr. R. Brian Haynes, editor, *ACP Journal Club*, and in the departments of Clinical Epidemiology and Biostatistics and of Medicine, McMaster University, Hamilton, Ont.: personal communication, 1994), including pediatrics.²² The Cochrane Pregnancy and Childbirth Database consists of regularly updated systematic reviews of controlled trials of obstetric care.²³ The Cochrane Collaboration was formed recently to meet the need for systematic, up-to-date reviews of controlled trials of all forms of health care and to make this information readily available to clinicians and other decision makers at all levels of health care systems.²⁴

Although these resources make the tasks of coping with the medical literature and practising evidence-based medicine more manageable, they do not eliminate the need for clinicians to be critical consumers of scientific information. However, we have found that, with a little experience, critical reading not only provides the basis for improved quality of care but also is empowering and fun.¹⁰

What are the expected outcomes?

After valid research is located or the quality of the available evidence is determined the next step is to estimate the expected consequences of the options being considered. In general there are three categories of outcomes: expected benefits, potential harms and costs.

For therapeutic and preventive interventions it is useful to consider the effects of treatment in absolute terms. For instance, the clinical importance of a reduction in relative risk depends on the baseline risk and the severity of the consequences of lack of treatment. If the baseline risk of a stroke in a certain population is 50%, a 20% reduction in relative risk would result in the prevention of one stroke for every 10 patients treated and would probably be considered worth while. On the other hand, if the baseline risk is 0.1%, a 20% reduction in risk would result in the prevention of one stroke for every 5000 patients. Results of research are often reported as relative risks or similar measures, which do not convey clinical importance.²⁵ However, it is possible to translate results into more clinically relevant measures, such as the number needed to treat, by considering the baseline risk.²⁶

For diagnostic tests the cardinal question is whether the test results can affect the estimated probability that a patient has a condition sufficiently to influence clinical action. If this probability is very high or very low, ordering a test is generally less likely to add useful information. Just as it is important to consider the baseline risk and the severity of consequences for therapeutic and preventive interventions, it is important to consider the before-test probability, the value of subsequent clinical actions, the potential harms and benefits, and the costs for a diagnostic intervention (Fig. 2). For example, if adverse consequences are associated with false-positive results of screening tests (e.g., screening for occult blood for early detection of colorectal cancer) the test must have good specificity. Conversely, if only minor adverse consequences are associated with false-positive results of screening tests (e.g., screening for phenylketonuria) but a missed diagnosis is associated with severe consequences, the test's sensitivity is more important than its specificity.

When considering costs, societal costs and costs borne by the patient must be distinguished. In general, costs borne by the patient should be considered in relation to his or her situation. However, for a clinician to make a judgement about societal costs within the context of a consultation is in conflict with his or her role in providing care. For example, a clinical practice guideline may recommend against routine ultrasound screening in pregnancy because the proven benefits are small and the costs are substantial.²⁷ However, such a guideline should be determined in relation to a group or population of patients. In the absence of such guidelines, clinicians are in

Table 2: Criteria for identifying valid articles*

| Type of article | Criteria |
|---|---|
| Trial of therapy or preventive intervention | Random assignment of patients to treatment groups; accountability of all patients at end of trial |
| Trial of diagnostic test | Independent, blind comparison with a gold standard; appropriate number of patients included |
| Trial of health service intervention | Random assignment of patients to comparison groups; reporting of clinically important outcomes for all participants |
| Review | Clearly focused question addressed; appropriate criteria used to select articles for inclusion |
| Clinical practice guidelines | Options and outcomes clearly specified; explicit process to identify, select and combine evidence |

*Adapted from Oxman, Sackett and Guyatt.¹⁵ Guides for critical appraisal and application of the medical literature have been described in detail elsewhere.^{15,18,19}

conflict if they try to consider societal costs when making decisions regarding specific patients.

What are the trade-offs?

The last step is to weigh the benefits against the harms and costs. This typically involves comparing widely different outcomes, such as reduced risk of illness, side effects of drugs, the patient burden of taking medication daily and the cost of drugs. Clearly, the value attached to a major stroke is different from that assigned to a mild side effect such as dizziness. Although it is obvious that these outcomes have different values, their relative values are less apparent. They are also likely to vary from one patient to another. For example, women with breast cancer provided with the same information about the benefits and harms of chemotherapy have different preferences and make different decisions about their treatment.²⁸ The same is true for men considering surgical treatment of symptomatic, benign hypertrophy of the prostate²⁹ and women considering hormone replacement therapy.³⁰

In general, decisions that depend on the relative value attached to the main consequences of a decision should be left to the patient. In such situations the clinician's role is to assist the patient in arriving at a decision, not to make a decision for the patient.

However, sometimes patients want physicians to make decisions for them.³¹ In these and other circumstances societal preferences can be important guides for clinical decisions, particularly when the benefits are small relative to societal costs. Such preferences are also important in clinical decisions about problems that affect people other than the patient (e.g., some communicable diseases and psychiatric problems) or that affect children, about terminally ill patients and about unsolicited preventive interventions.

For many clinical decisions it is impractical and un-

necessary to quantify the values attached to the consequences. However, in the same way that it is important for evidence and expected outcomes to be explicit, judgements of preference in weighing benefits against harms and costs should also be explicit.^{8,32}

How should the problem be managed?

Although clinical decisions often seem black and white (e.g., to prescribe a drug or not) there is usually a range of options from always doing something to never doing it (Fig. 3). In addition, there are almost always caveats when implementing a guideline. For example, contraindications of or exemptions from preventive and therapeutic interventions are common. Sometimes a

| Option | Example |
|------------------|---|
| Least aggressive | <ul style="list-style-type: none"> Do not treat; refuse treatment if requested. |
| | <ul style="list-style-type: none"> Recommend against treatment, but treat if requested. |
| | <ul style="list-style-type: none"> Treat patients at high risk. |
| | <ul style="list-style-type: none"> Present pros and cons of treatment to all affected patients. |
| | <ul style="list-style-type: none"> Screen patients to determine need for treatment; treat all affected patients. |
| Most aggressive | <ul style="list-style-type: none"> Screen patients and conduct outreach; make efforts to ensure compliance. |

Fig. 3: "Shades of grey" in treatment recommendations contained in clinical practice guidelines.

| | | Gold standard | |
|-----------------|---|---|---|
| | | + | - |
| Diagnostic test | + | <p>True-positive results</p> <p>Benefits: from follow-up Harms: from test and follow-up, anxiety Costs: test and follow-up</p> | <p>False-positive results</p> <p>Benefits: none Harms: from test and follow-up, anxiety Costs: test and follow-up</p> |
| | - | <p>False-negative results</p> <p>Benefits: none Harms: from test and delayed diagnosis Costs: test and consequences of delayed diagnosis</p> | <p>True-negative results</p> <p>Benefits: reduced anxiety and avoidance of unnecessary treatment Harms: from test Cost: test and savings from avoiding unnecessary treatment</p> |

Fig. 2: Benefits, harms and costs of diagnostic tests.

guideline must be adjusted to take into account patient characteristics (e.g., socioeconomic status) or characteristics of the local setting (e.g., availability of resources).

If clinicians focus on common problems, as we have suggested,⁹ they are likely to find more than one guideline for interventions. Whether clinicians develop their own guideline or determine whether a guideline is valid and applicable in their practice, they must recognize any conflicts with other guidelines for the same clinical problem. If possible, clinicians should identify the extent to which differences in recommendations are due to differences in how the problem was framed, how the evidence was assessed, how outcomes were estimated or how judgements about preferences were made.

If a clinical practice guideline is not explicit about each of these steps it is difficult, if not impossible, to determine the source of conflict. Therefore, it makes sense to search for guidelines that are explicit and to be explicit about guidelines developed in or adapted to one's practice. Many organizations have begun to publish structured summaries of their guidelines,³³ which should help ensure that they include at least some description of how a recommendation was derived. An outline of how

we summarize clinical practice guidelines is shown in Table 3.

Because medical knowledge and practice environments evolve continually, guidelines have a "shelf life" after which they should be reassessed. More important, the determination of interventions for a significant problem is of little benefit to our patients if guidelines just sit on a shelf. In the next two articles in this series we will discuss strategies for measuring what physicians are doing and implementing guidelines to close any gaps between what they should be doing and what they are doing.

The next article will focus on decisions made in measuring clinical performance: what to measure, whether the information needed to make the measurement is available, how to select an appropriate sample of patients, how to collect the information needed and how to interpret the information collected.

References

1. Battista RN, Hodge MJ: Clinical practice guidelines: between science and art. *Can Med Assoc J* 1993; 148: 385-389
2. Oxman AD: Coordination of guidelines development. *Can Med Assoc J* 1993; 148: 1285-1288
3. SHEP Cooperative Research Group: Prevention of stroke by anti-hypertensive drug treatment in older persons with isolated systolic hypertension: final results of the systolic hypertension in the elderly program (SHEP). *JAMA* 1991; 265: 3255-3264
4. Haynes RB, Lacourcière Y, Rabkin SW et al: Report of the Canadian Hypertension Society Consensus Conference: 2. Diagnosis of hypertension in adults. *Can Med Assoc J* 1993; 149: 409-418
5. Eddy DM: Clinical policies and the quality of clinical practice. *N Engl J Med* 1982; 307: 343-347
6. Eddy DM: Practice policies: guidelines for methods. *JAMA* 1990; 263: 1839-1841
7. Hayward RSA, Laupacis A: Initiating, conducting and maintaining guidelines development programs. *Can Med Assoc J* 1993; 148: 507-512
8. Eddy DM: Guidelines for policy statements: the explicit approach. *JAMA* 1990; 263: 2239-2243
9. Evidence-Based Care Resource Group: Evidence-based care: 1. Setting priorities: How important is this problem? *Can Med Assoc J* 1994; 150: 1249-1254
10. Evidence-Based Medicine Working Group: Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA* 1992; 268: 2418-2425
11. Williamson JW, Goldschmidt PG, Colton T: The quality of medical literature: an analysis of validation assessments. In Bailar JC, Mosteller F (eds): *Medical Uses of Statistics*. NEJM Books, Waltham, Mass, 1986: 370-391
12. Antman EM, Lau J, Kupelnick B et al: A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: treatments for myocardial infarction. *JAMA* 1992; 268: 240-248
13. Williamson JW, German PS, Weiss R et al: Health science information management and continuing education of physicians. *Ann Intern Med* 1989; 110: 151-160
14. Oxman AD, Guyatt GH: The science of reviewing research. *Ann N Y Acad Sci* 1993; 703: 125-134
15. Oxman AD, Sackett DL, Guyatt GH for the Evidence-Based Medicine Working Group: Users' guides to the medical literature. I: How to get started. *JAMA* 1993; 270: 2093-2095

Table 3: Outline for summarizing clinical practice guidelines

| |
|--|
| Date: Date of last revision |
| Authors: Relevant authors |
| Targeted patients: Main characteristics of targeted patients |
| Main options considered: Main interventions, including screening tests, patient education, other preventive interventions, diagnostic tests or therapeutic interventions |
| Main outcomes considered: Main consequences of intervention, including potential benefits, harms and costs |
| Evidence: Brief summary of main evidence including only key citations (best overviews and critical studies) and indication of strength of the evidence |
| Recommendation: Succinct statement (one to three sentences) of proposed policy |
| Expected benefits, harms and costs: Quantitative or qualitative estimate of main consequences that led to recommendation |
| Preference judgements: Identification of key considerations concerning patient preferences for the expected outcomes |
| Other guidelines: Reference to other guidelines and consistency with them |
| Dissenting opinions: Identification of any disagreement among professional staff and main source of disagreement |
| Caveats: Identification of any important caveats |
| Implementation: Specification of primary implementation strategies |
| Evaluation: Statement of any plans for evaluating impact of clinical policy |
| Information sources: Main strategies used to identify evidence |
| Key references: Applicable references |

16. Oxman AD, Guyatt GH: Guidelines for reading literature reviews. *Can Med Assoc J* 1988; 138: 697-703
17. Oxman AD, Cook DJ, Guyatt GH for the Evidence-Based Medicine Working Group: Users' guides to the medical literature. VI: How to use an overview. *JAMA* (in press)
18. Sackett DL, Haynes RB, Guyatt GH et al: The interpretation of diagnostic data. In *Clinical Epidemiology: a Basic Science for Clinical Medicine*, Little, Brown and Company, Boston, 1991: 69-152
19. Purpose and procedure. *ACP J Club* 1991; Jan-Feb 1991: A6-A7 (*Ann Intern Med* 114, suppl 1)
20. Chalmers I, Hetherington J, Elbourne D et al: Materials and methods used in synthesizing evidence to evaluate the effects of care during pregnancy and childbirth. In Chalmers I, Enkin M, Keirse MJNC (eds): *Pregnancy and Childbirth*, Oxford University Press, Oxford, England, 1989: 39-66
21. Sinclair JC, Bracken MB (eds): *Effective Care of the Newborn Infant*, Oxford University Press, Oxford, England, 1992: 3-18
22. Moyer V: Spreading the Journal Club net — pediatrics. *Clin Epidemiol News* 1993; 12: 13
23. Enkin MW, Keirse MJNC, Renfrew MJ et al (eds): *Cochrane Pregnancy and Childbirth Database [derived from the Cochrane Database of Systematic Reviews]*, Cochrane Updates on Disk, Update Software, Oxford, England, 1993: disk issue 2
24. *The Cochrane Collaboration* [brochure], UK Cochrane Centre, National Health Service Research and Development Programme, Oxford, England, 1993
25. Naylor CD, Chen E, Strauss B: Measured enthusiasm: Does the method of reporting trial results alter perceptions of therapeutic effectiveness? *Ann Intern Med* 1992; 117: 916-921
26. Laupacis A, Sackett DL, Roberts RS: An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988; 318: 1728-1733
27. Neilson JP: Routine ultrasonography in early pregnancy. In Enkin MW, Keirse MJNC, Renfrew MJ et al (eds): *Cochrane Pregnancy and Childbirth Database [derived from the Cochrane Database of Systematic Reviews]* (review no 03872, Mar 24, 1993), Cochrane Updates on Disk, Update Software, Oxford, England, 1993: disk issue 2
28. Levine MN, Gafni A, Markham B et al: A bedside decision instrument to elicit a patient's preference concerning adjuvant chemotherapy for breast cancer. *Ann Intern Med* 1992; 117: 53-58
29. Barry MJ, Mulley AG, Fowler FJ et al: Watchful waiting vs immediate transurethral resection for symptomatic prostatism: the importance of patients' preferences. *JAMA* 1988; 259: 3010-3017
30. American College of Physicians: Guidelines for counseling postmenopausal women about preventive hormone therapy. *Ann Intern Med* 1992; 117: 1038-1041
31. Degner LF, Sloan JA: Decision making during serious illness: What role do patients really want to play? *J Clin Epidemiol* 1992; 45: 941-950
32. Eddy DM: Anatomy of a decision. *JAMA* 1990; 263: 441-443
33. Hayward RSA, Tunis SR, Wilson MC et al: More informative abstracts of articles describing clinical practice guidelines. *Ann Intern Med* 1993; 118: 731-737

CYTOTEC® (misoprostol) 100 µg / 200 µg

Therapeutic Classification Mucosal Protective Agent

INDICATIONS CYTOTEC (misoprostol) is indicated for the prevention of NSAID-induced gastric ulcers. Patients at high risk of developing NSAID-induced complications and who may require protection include: • Patients with a previous history of ulcer disease or a significant gastrointestinal event. • Patients over 60 years of age. • Patients judged to be at risk because of general poor health, severe concomitant medical disease, or patients who are poor surgical risks. • Patients disabled by joint symptoms (e.g., HAQ Disability Index Score >1.5) or those with severe systemic manifestations of arthritis. • Patients taking other drugs known to damage or exacerbate damage to the gastrointestinal tract such as corticosteroids or anticoagulants. • Patients taking a high dosage of multiple NSAIDs, including those available Over-The-Counter. The risk of NSAID-induced complications may be highest in the first three months of NSAID therapy. CYTOTEC is also indicated for the treatment of NSAID-induced gastric ulcers (defined as ≥ 0.3 cm in diameter) and for the treatment of duodenal ulcers.

CONTRAINDICATIONS Known sensitivity to prostaglandins, prostaglandin analogues, or excipients (microcrystalline and hydroxypropyl methylcellulose, sodium starch glycolate and hydrogenated castor oil). Contraindicated in pregnancy. (See CLINICAL PHARMACOLOGY.) Women should be advised not to become pregnant while taking CYTOTEC (misoprostol). If pregnancy is suspected, use of the product should be discontinued.

WARNINGS Women of childbearing potential should employ adequate contraception (i.e., oral contraceptives or intrauterine devices) while receiving CYTOTEC (misoprostol). (See CONTRAINDICATIONS.) **Nursing Mothers:** It is unlikely that CYTOTEC is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, CYTOTEC should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants. **Pediatric Use:** Safety and effectiveness in patients below the age of 18 have not been established.

PRECAUTIONS **Selection of Patients:** Caution should be used when using symptomatology as the sole diagnostic and follow-up procedure, since CYTOTEC (misoprostol) has not been shown to have an effect on gastrointestinal pain or discomfort. Before treatment is undertaken, a positive diagnosis of duodenal ulcer or NSAID-induced gastric ulcer should be made. The general health of the patient should be considered. Misoprostol is rapidly metabolized by most body tissues to inactive metabolites. Nevertheless, caution should be exercised when patients have impairment of renal or hepatic function. (See CLINICAL PHARMACOLOGY.) **Pharmacokinetics:** **Diarrhea:** Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as irritable bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if CYTOTEC is prescribed. **Use in Elderly or Renally Impaired: Considerations for Dosage Adjustment:** In subjects over 64 years of age or those who are renally impaired the pharmacokinetics may be affected, but not to a clinically significant degree. (See DOSAGE AND ADMINISTRATION.) No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 µg QID) is recommended. **Drug Interactions:** The serum protein binding of misoprostol acid, the active metabolite of misoprostol was not affected by: indomethacin, ranitidine, digoxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, acetaminophen, ibuprofen, chlorpromazine, and hydrochlorothiazide. Salicylic acid (300 µg/mL) lowered the protein binding of misoprostol from 84% to 52%; this is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short. In laboratory studies, misoprostol has shown no significant effect on the cytochrome P450-linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolized by this system. No drug interactions attributable to misoprostol have been observed to date. (See CLINICAL PHARMACOLOGY.) Some prostaglandins and prostaglandin analogues have the capacity to produce hypotension through peripheral vasodilation. The results of clinical trials to date indicate that CYTOTEC has not produced hypotension at dosages effective in promoting the healing of ulcers. Nevertheless, CYTOTEC should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g., cerebral vascular disease or coronary artery disease. Epileptic seizures have been reported with prostaglandins and prostaglandin analogues administered by routes other than oral. Therefore, misoprostol tablets should be used in known epileptics only when their epilepsy is adequately controlled and then only when expected benefits outweigh potential risks. Symptomatic responses to CYTOTEC do not preclude the presence of gastric malignancy.

ADVERSE REACTIONS **Gastrointestinal:** In subjects receiving CYTOTEC (misoprostol) 400 or 800 µg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea, abdominal pain and flatulence. The average incidences of these events were 11.4%, 6.8% and 2.9%, respectively. In clinical trials using a dosage regimen of 400 µg bid, the incidence of diarrhea was 12.6%. The events were usually transient and mild to moderate in severity. Diarrhea, when it

occurred, usually developed early in the course of therapy, was self limiting and required discontinuation of CYTOTEC in less than 2% of the patients. The incidence of diarrhea can be minimized by adjusting the dose of CYTOTEC, by administering after food, and by avoiding co-administration of CYTOTEC with magnesium-containing antacids. **Gynecological:** Women who received CYTOTEC during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). **Elderly:** There were no significant differences in the safety profile of CYTOTEC in approximately 500 ulcer patients who were 65 years of age or older, compared with younger patients. Confusion has been reported in a small number of patients in our post marketing surveillance of CYTOTEC. Incidence greater than 1%. In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving CYTOTEC and may be causally related to the drug: nausea (3.2%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%) and constipation (1.1%). However, there were no clinically significant differences between the incidences of these events for CYTOTEC and placebo.

DOSAGE AND ADMINISTRATION **Treatment and Prevention of NSAID-Induced Gastric Ulcers:** The recommended adult oral dosage of CYTOTEC (misoprostol) for the prevention and treatment of NSAID-induced gastric ulcer is 400 to 800 µg a day in divided doses. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate, CYTOTEC and NSAIDs are to be taken simultaneously. CYTOTEC should be taken after food. **Duodenal Ulcer:** The recommended adult oral dosage of CYTOTEC (misoprostol) for duodenal ulcer is 800 µg per day for 4 weeks in two or four equally divided doses (i.e., 200 µg qid or 400 µg bid). The last dose should be taken at bedtime with food. Antacids (aluminum based) may be used as needed for relief of pain. Treatment should be continued for a total of 4 weeks unless healing in less time has been documented by endoscopic examination. In the small number of patients who may not have fully healed after 4 weeks, therapy with CYTOTEC may be continued for a further 4 weeks. **Use in Elderly and Renally Impaired: Consideration for Dosage Adjustment:** Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $T_{1/2}$, C_{max} and AUC compared to normals. There was no clear correlation between degree of impairment and AUC. In subjects over 64 years of age the pharmacokinetics may be affected. In both patient groups the pharmacokinetic changes are not clinically significant. No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 µg QID) is recommended.

AVAILABILITY CYTOTEC (misoprostol) 200 µg tablets are white to off-white, scored, hexagonal with SEARLE 1461 engraved on one side available in bottles of 120 and 500 tablets. CYTOTEC 100 µg tablets are white to off-white, round tablets with SEARLE engraved on one side and CYTOTEC on the other available in bottles of 100 tablets.

Store below 30°C (86°F).

Pharmacist: Dispense with Patient Insert.

400 Iroquois Shore Road
Oakville, Ontario
L6H 1M5

SEARLE

References: 1. Elliott DP. *Annals of Pharmacotherapy* 1990;24:954-957. 2. Agrawal NW, et al. *Annals of Internal Medicine* 1991;115(3):195-200. 3. Cryer B, Feldman M. *Arch Intern Med* June 1992;152:1145-1153. 4. Fries JF, J of Musculoskeletal Medicine 1991;2:21-28. 5. Gabriel SE, et al. *Annals of Internal Medicine* 1991;115(10):787-796. 6. CYTOTEC® Product Monograph, Searle Canada Inc. 7. Graham DY, Agrawal NM, Roth SH. *The Lancet* 1988;2:1277-1280. Product Monograph available upon request.

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Proven Protection
CYTOTEC® B.I.D.
(misoprostol) 200 µg WITH FOOD