SOUNDING BOARD

Potential Pitfalls of Disease-Specific Guidelines for Patients with Multiple Conditions

Mary E. Tinetti, M.D., Sidney T. Bogardus, Jr., M.D., and Joseph V. Agostini, M.D.

Quality-assurance initiatives encourage adherence to evidenced-based guidelines for the management of particular diseases and ensure that such adherence is monitored.[1-3] The best of these guidelines, developed by national organizations, systematically collect the available evidence regarding a given disease and provide recommendations, including the use of multidrug regimens, for the treatment of patients with that disease.[4-8] The goal is to maximize benefits to patients with specific diseases by encouraging standardization among providers of health care.[1,2] The push for financial incentives linked to performance will probably accelerate the movement toward the guideline-driven prescribing of medications.[1,2]

The expected benefits, including the prevention of disease-specific outcomes, deaths, and hospitalizations, that are avoided because of adherence to disease-specific guidelines for the prescribing of medications have been well chronicled.[2] No one doubts the benefit, for example, of beta-blockers in the prevention of recurrent myocardial infarctions[7] or of angiotensin-converting–enzyme (ACE) inhibitors in retarding the loss of renal function.[5] Some multidrug regimens clearly provide added disease-specific benefits for at least some subpopulations of patients, as compared with single-drug therapy.[4,5,8]

Less clear, however, are the long-term net benefits and harm associated with the combination of all medications that are taken in adherence to disease-specific guidelines for patients with several coexisting health conditions. Since 20 percent of Medicare beneficiaries have five or more chronic conditions[9] and 50 percent are receiving five or more medications,[10] this is not an inconsequential concern. Consider, for example, the case of a 70-year-old woman who has the common combination of hypertension, myocardial infarction, depression, diabetes mellitus, and osteoporosis. Adherence to disease guidelines might require this patient to take an aspirin, an ACE inhibitor, a beta-blocker, a bisphosphonate, calcium, a diuretic, a selective serotonin-reuptake inhibitor, a statin, a sulfonylurea drug, perhaps a thiazolidinedione, and vitamin D.[4-8] These guideline-driven medications are taken in addition to prescription and over-the-counter drugs for conditions such as allergies, pain, dyspepsia, and insomnia. Viewing disease-specific medication guidelines from this perspective raises the question of whether what is good for the disease is always best for the patient.

All medications have the potential for harm as well as benefit. Furthermore, evidence is emerging that patients, particularly elderly patients and those with multiple conditions, vary in regard to the amount of importance they place on health outcomes such as longer survival, the prevention of specific disease events, and physical and cognitive functioning, as well as in the amount of inconvenience and risk of adverse effects they are willing to tolerate.[11-15] The developers of guidelines recognize that decisions about prescribing must be individualized, with patients' overall health taken into account. Nevertheless, one of the hallmarks of quality-assurance programs is a reduction in the variation of practice patterns among providers.[1-3] It is difficult to separate inappropriate variation due to neglect or ignorance on the part of providers from appropriate variation due to the total disease burden and the preferences of patients. A review of the evidence underlying disease-specific guidelines helps to explain the origin of the tension between the standardized treatment of diseases and the individualized care of patients with multiple conditions.

CHARACTERISTICS OF GUIDELINES

Guidelines characteristically begin with a presentation of the relative risk of death or of other adverse outcomes associated with the target disease. Diagnostic and therapeutic interventions, includ-

ing medications, are recommended to decrease these risks.[4-8] The randomized, controlled trials on which the recommendations are based typically provide evidence of modest reductions in the relative risk of the disease-specific outcomes that are associated with the use of individual medications and, in some cases, combinations of medications.[16,17] Older patients and patients with multiple health conditions have been excluded from many evidence-generating randomized, controlled trials.[17,18] Arguments have been made for extrapolating the evidence from such trials to subpopulations of elderly patients,[19] but the generalizability of the results to the types of patients who have been excluded from trials because of their multiple health conditions remains unknown for many medications.[17,18]

Adverse events are evaluated with less rigor and precision than are benefits in most randomized, controlled trials.[20] The mention of harm in guidelines is necessarily limited to a few well-known effects of individual medications, such as the electrolyte or renal abnormalities associated with diuretics or ACE inhibitors.[4,8]

Coexisting conditions are acknowledged in guidelines if they increase the risks associated with the target disease or affect its treatment or prognosis.[4,5,7,8] The presence of coexisting diseases often results in recommendations for additional medications, although selecting among medication options on the basis of specific combinations of diseases may also reduce the total number of medications required for multiple coexisting conditions.[4,5,7,8] Drug recommendations for patients with multiple conditions are presented but rarely rated in terms of priority. With notable exceptions such as end-of-life care for patients with congestive heart failure, the health preferences of patients and the outcomes related to their quality of life are seldom mentioned.[8]

The clinical trials supporting the medication recommendations that are included in guidelines are conducted over a few months or a few years. The short-term nature of the trials precludes the ability to detect the benefit or harm associated with such medications when consumed over decades for the treatment of chronic diseases. The possible increase in the severity of prostate cancer in patients treated with finasteride, for example, was a fortuitous observation.[21] How many other such unpredictable consequences of medications have gone undetected? The assumption that medications, either individually or in combination, are well tolerated stems, at least in part, from a lack of effort to prove otherwise. The potential for undetected adverse long-term consequences is a particular concern for patients with multiple conditions, who are exposed to ever-increasing numbers of medications and whose response to medications may be altered by the presence of coexisting conditions.

UNANSWERED QUESTIONS

The medication-related evidence underlying treatment guidelines best addresses the short-term, disease-specific benefits of individual medications, and some combinations of medications, for persons who resemble the participants in randomized, controlled trials and who take their medications as prescribed. Many important clinical questions remain unanswered. For example, how is the adherence to drug regimens affected by the need to follow guidelines for the treatment of multiple coexisting conditions? We know that patients take only about half of their medications as prescribed and that adherence decreases as the number of medications increases.[22]

Other compelling but unanswered questions include the following: How much of what type of benefit can be expected from various combinations of medications, with what risk of various adverse effects? Over what period of time? How is the benefit-to-harm ratio altered in the face of multiple coexisting conditions and medications? How are individual patients' preferences incorporated into the prescribing of guideline-driven medications in clinical practice?

Guidelines and quality-assurance initiatives largely ignore the issue of the marginal benefits of multiple medications as recommended both within and among various sets of guidelines. What added benefit (without added harm) does the seventh, eighth, or ninth medication provide over the second or third? What additional benefits, over what expected time period, will accrue, for example, for a 75-year-old man with depression, insomnia, hypertension, chronic pain from arthritis, and diabetes, when a thiazolidinedione is added to 10 preexisting medications? What is the additional risk of adverse effects?

We know that increasing numbers of medications are associated with an increased risk of adverse events.[23] Although some classes of drugs entail particularly high risks, the prevalence of ad-

verse events is roughly proportional to the frequency of their use. Cardiovascular drugs, for example, account for about 25 percent of known adverse events, probably because they are the most commonly prescribed class of drugs.[24] The known relationship between adverse events and multiple medications should certainly prompt physicians to balance the expected benefits with known adverse events. The prevalence of problems associated with multiple medications is probably underestimated, since the available data reflect only the adverse effects that have already been characterized and not the broader physical, cognitive, psychological, and other effects that remain unknown and unexplored.

Individual medications that impart disease-specific benefits may be less beneficial, or even harmful, when taken along with other medications by patients with multiple coexisting conditions and variable health outcomes. Few physicians would advocate tight glucose control in patients with terminal cancer. What about less obvious but more common situations? Is a statin or beta-blocker, for example, as part of an 11-drug regimen, likely to provide greater benefit or greater harm to a 73-year-old whose priority is maximal energy, strength, and alertness today and who is willing to take on an increased risk of myocardial infarction or stroke over the next 5 or 10 years?

The proliferation of multidrug regimens demands that we consider health priorities as well as the marginal benefit and harm associated with all medications when translating disease guidelines into prescribing decisions for individual patients with multiple health conditions. Such an evolution from a disease-driven to a patient-driven focus requires an investment in research and changes in the development of guidelines, in the measurement of quality, and in clinical decision making.

THE NEED FOR RESEARCH

Expense and complexity notwithstanding, basic and clinical research is needed to determine the effects of multiple medications that act simultaneously and to decipher how these effects are altered by genetic, physiological, disease-related, and other factors.[25] Multidrug regimens need to be compared directly with simpler regimens in randomized, controlled trials or in appropriately designed observational studies.[26,27] The full spectrum of patients expected to use the medications should participate, including those with multiple conditions who consume large numbers of drugs. The evaluation of a broad range of carefully measured physical, psychological, cognitive, and other outcomes should be standard so that disease guidelines and clinical decisions can integrate patients' preferences and the tradeoffs patients are willing to make in terms of the risk of various health outcomes.

CHANGES IN DISEASE GUIDELINES

Transparency of the evidence, collaboration, and integration are elements critical to high-quality health care,[1,2] and the incorporation of these elements into disease-specific guidelines could help inform the prescribing of medications for patients with multiple conditions. Limiting the recommendations to regimens and subpopulations of patients for which there is compelling evidence that the benefit outweighs any harm would enhance the transparency of guidelines. This requirement might also encourage researchers to tackle the complex questions discussed earlier. Studies that show the benefit of one drug for one outcome in selected patients are considered acceptable levels of evidence and curb the motivation to invest the time, expense, and effort necessary to conduct the more complex studies needed.

Both benefit and harm could be presented on absolute, rather than relative, scales or with measurements such as the number needed to treat (or harm), which are more appropriate for clinical interpretation than are reductions in relative risk.[13,28] For example, in the treatment of hypertension in elderly patients, a 30 percent reduction in risk is more transparently reported as a reduction in the likelihood of a stroke during the next 10 years from 10 percent to 7 percent.[29] If the data are available, benefit and harm should be presented for various categories of outcomes, subpopulations, and follow-up times. The last ensures that the time frame for an expected benefit is within a patient's anticipated lifetime and also respects the fact that many patients consider the amount of time that will elapse until an expected outcome when deciding whether to take medications.[14,15] If such data are unavailable, transparency would dictate that this absence be revealed.

The national disease and quality-assurance organizations could collaboratively review the evidence concerning the benefit and harm of medica-

tions that are recommended for the treatment of various diseases. With an eye toward maximizing benefits while minimizing the unfavorable consequences of multiple medications on adherence and patient health, these organizations could agree on, and report, the priorities involved in the prescribing of medications for multiple conditions.

DISEASE GUIDELINES AND PRESCRIPTION DECISIONS

Making decisions about medications for patients with multiple conditions requires an optimal tradeoff between benefit and harm within the context of patients' health priorities. Such decision making depends on an accurate and complete presentation of the evidence — of the absolute benefit and harm over time with respect to a spectrum of outcomes — along with a discussion of preferences and tradeoffs. The successful translation of disease guidelines into prescriptions that meet the needs of individual patients hinges on the use of information technology to collect, analyze, and present complex data. Success also depends on effective communication between physicians and patients.[13]

Attention to patients' medication-related perceptions and priorities can also help physicians to prescribe appropriately.[15] Although clinicians focus on disease-specific outcomes such as the prevention of stroke or the maintenance of disease-free intervals, the priorities of patients are more variable, particularly when multiple health conditions are present.[11,12] Physicians recommend treatments that have less expected benefit than many patients desire when deciding whether to take medications.[14,30] Furthermore, although physicians focus primarily on benefits when making decisions about medication and communicating those decisions, patients consider side effects and other factors such as time to an effect, convenience, and cost in deciding whether to start or continue medications.[14,31]

Determining how best to resolve the inherent tension between prescribing for the disease and prescribing for the patient remains a challenge. It may seem naive to expect investigators, the developers of guidelines, physicians, or patients to embrace this challenge in light of the complexity involved and the many issues relating to health and medication that compete for attention. Ignoring the conflicts between the disease-driven and patient-driven use of medication, however, puts us at risk for allowing the accumulated harm due to the burden of medication to outstrip the benefits.

Supported in part by a grant (P60AG10469) to the Yale Pepper Center from the National Institute on Aging. Dr. Agostini is the recipient of a Veterans Affairs Health Services Research Career Development Award and a Merck/American Federation for Aging Research Junior Investigator Award in Geriatric Clinical Pharmacology.

We are indebted to Dr. Leo Cooney, who reviewed an early draft of this article.

From the Departments of Internal Medicine (M.E.T., S.T.B., J.V.A.) and Epidemiology and Public Health (M.E.T.), Yale School of Medicine, New Haven, Conn.; and the Clinical Epidemiology Research Center, Veterans Affairs Connecticut Healthcare System, West Haven, Conn. (J.V.A.).

1. Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, D.C.: National Academies Press, 2001.
2. The state of health care quality: 2003. Washington, D.C.: National Committee for Quality Assurance, 2003.
3. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;348:2635-45.
4. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.
5. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002;25:S33-S49.
6. National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Belle Mead, N.J.: Excerpta Medica, 1999. (Accessed December 3, 2004, at http://www.nof.org/physguide.)
7. Smith SC Jr, Blair SN, Bonow RO, et al. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 2001;104:1577-9.
8. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. Circulation 2001;104:2996-3007.
9. Berenson RA, Horvath J. Confronting the barriers to chronic care management in Medicare. Bethesda, Md.: Health Affairs, January 22, 2003 (Web exclusive). (Accessed November 18, 2004, at http://content.healthaffairs.org/cgi/content/full/hlthaff.w3.37v1/DC1.)
10. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA 2002;287:337-44.
11. Tsevat J, Dawson NV, Wu AW, et al. Health values of hospitalized patients 80 years or older. JAMA 1998;279:371-5.
12. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med 2002;346:1061-6.
13. Epstein RM, Alper BS, Quill TE. Communicating evidence for participatory decision making. JAMA 2004;291:2359-66.
14. Berry DC, Michas IC, Gillie T, Forster M. What do patients want to know about their medicines and what do doctors want to tell them? A comparative study. Psychol Health 1997;12:467-80.
15. Elwyn G, Edwards A, Britten N. What information do patients need about medicines? "Doing prescribing": how doctors can be more effective. BMJ 2003;327:864-7.
16. Peto R, Baigent C. Trials: the next fifty years: large scale randomised evidence of moderate benefits. BMJ 1998;317:1170-1.

17. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? JAMA 1994;271:59-63.
18. Gross CP, Mallory R, Heiat A, Krumholz HM. Reporting the recruitment process in clinical trials: who are these patients and how did they get there? Ann Intern Med 2002;137:10-6.
19. Alter DA, Manuel DG, Gunraj N, Anderson G, Naylor CD, Laupacis A. Age, risk-benefit trade-offs, and the projected effects of evidence-based therapies. Am J Med 2004;116:540-5.
20. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. JAMA 2001;285:437-43.
21. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215-24.
22. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials on interventions to assist patients to follow prescriptions for medications. Lancet 1996;348:383-6. [Erratum, Lancet 1997;349:1180.]
23. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. N Engl J Med 2003;348:1556-64.
24. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107-16.
25. Evans WE, McLeod HL. Pharmacogenomics — drug disposition, drug targets, and side effects. N Engl J Med 2003;348:538-49.
26. Ioannidis JP, Haidich AB, Pappa M, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. JAMA 2001;286:821-30.
27. Vandenbrouke JP. When are observational studies as credible as randomized trials? Lancet 2004;363:1728-31.
28. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-91.
29. Gueyffier F, Bulpitt C, Boissel J-P, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. Lancet 1999;353:793-6.
30. Lewis DK, Robinson J, Wilkinson E. Factors involved in deciding to start preventive treatment: qualitative study of clinicians' and lay people's attitudes. BMJ 2003;327:841.
31. Townsend A, Hunt K, Wyke S. Managing multiple morbidity in mid-life: a qualitative study of attitudes to drug use. BMJ 2003;327:837.

***JOURNAL* INDEX**

The index to volume 351 of the *Journal* will be available on February 17, 2005. At that time, it can be downloaded free in PDF format from **www.nejm.org** or can be ordered in a printed and bound format. To order a bound copy, please call 1-800-217-7874 from the United States and Canada (call 651-582-3800 from other countries) or e-mail info@valeoip.com.