REVIEW ARTICLE

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Principles of Conservative Prescribing

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Judicious prescribing is a prerequisite for safe and appropriate medication use. Based on evidence and lessons from recent studies demonstrating problems with widely prescribed medications, we offer a series of principles as a prescription for more cautious and conservative prescribing. These principles urge clinicians to (1) think beyond drugs (consider nondrug therapy, treatable underlying causes, and prevention); (2) practice more strategic prescribing (defer nonurgent drug treatment; avoid unwarranted drug switching; be circumspect about unproven drug uses; and start treatment with only 1 new drug at a time); (3) maintain heightened vigilance regarding adverse effects (suspect drug reactions; be aware of withdrawal syndromes; and educate patients to anticipate reactions); (4) exercise caution and skepticism regarding new drugs (seek out unbiased information; wait until drugs have sufficient time on the market; be skeptical about surrogate rather than true clinical outcomes; avoid stretching indications; avoid seduction by elegant molecular pharmacology; beware of selective drug trial reporting); (5) work with patients for a shared agenda (do not automatically accede to drug requests; consider nonadherence before adding drugs to regimen; avoid restarting previously unsuccessful drug treatment; discontinue treatment with unneeded medications; and respect patients' reservations about drugs); and (6) consider long-term, broader impacts (weigh long-term outcomes, and recognize that improved systems may outweigh marginal benefits of new drugs).

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In striving to relieve suffering and prolong life, we often turn to medications. Drugs are the therapy physicians most frequently deploy, with more than 60% of people younger than 65 years receiving a prescription drug each year.[1,2] It is often impossible for patients and physicians alike to imagine ending a clinical encounter without a medication prescription. And for most doctors, it is equally unimaginable not to turn to the most up-to-date drugs in trying to do the right thing for the patient.

This desire to help patients with the "latest and greatest" drugs is congruent with the messages and interests of the pharmaceutical industry, but there is an alternate paradigm that represents a radical shift in prescribing attitudes and behaviors. Ironically, the term we believe best describes this paradigm is *conservative prescribing*. Although others have used labels such as *healthy skepticism*, *more judicious*, *rational*, *careful*, or *cautious prescribing*, we believe that the term *conservative prescribing* conveys an approach that goes beyond the oft-repeated physician's mantra, "first, do no harm."[3,4]

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The concept sums up lessons from past experience as well as from recent studies demonstrating that medications are commonly used inappropriately, overused,[5-8] and associated with significant harm—suggesting the need to more thoughtfully weigh claims for drugs, especially new drugs.[9] Conservative prescribing also embodies an important new construct—the precautionary principle—an ecologic paradigm that stresses *forecaring*, the practice of anticipating potential adverse effects, even when cause-effect relationships are not fully established scientifically.[10,11] This approach places the burden of proving safety on the proponents of introducing a new chemical into the human ecosystem and thus encourages exploring alternatives to new drugs.

Mastering conservative prescribing is especially important for young physicians and trainees, who lack historical knowledge of past drug harms and withdrawals from the market. Early in their careers, when prescribing habits are being formed, they may rarely have encountered patients with serious drug-related problems or rarely experienced the anguish of realizing that a drug they prescribed harmed or even killed a patient. Learning to prescribe, like learning to perform a procedure or becoming facile in physical examination, is a skill. This important skill is often relegated to a few pharmacology lectures on pharmacokinetics or dosing.[12,13] However, unlike other procedural or physical examination skills, prescribing is often driven by pharmaceutical marketing and by patients requesting drugs they hear advertised.[14,15] To counterbalance these prescribing pressures, which include often unrealistic patient expectations, practice time constraints, and paucity of data and practical guidance, our team of physicians, pharmacists, and educators has identified principles for safer and more evidence-based prescribing.

THINK BEYOND DRUGS

Seek Nondrug Alternatives First

Rather than mainly prescribing drugs, clinicians should broaden their repertoire to become more skilled and effective at counseling and prescribing exercise, physical therapy, diet changes, smoking cessation, orthotics, or surgery when appropriate. Substantial literature supports initiating nonpharmacologic measures as initial or preferred therapy for a range of conditions commonly treated with drugs, such as hypertension,[16,17] diabetes,[18] insomnia,[19] back pain,[20] arthritis,[21] and headache.[22]

Consider Potentially Treatable Underlying Causes of Problems Rather Than Just Treating the Symptoms With a Drug

Could elevated cholesterol be hypothyroidism?[23] Might impotence be a sign of marital discord, a pituitary problem, diabetes, or drug induced? Could "arthritis" pain represent osteomalacia (perhaps due to celiac sprue),[24] occupational trauma (requiring workplace redesign),[25] or a drug effect?[26] Before reaching for a statin, erectile dysfunction agent, or a nonsteroidal anti-inflammatory drug (NSAID), consider the underlying cause rather than just treating or masking symptoms.

Look for Opportunities for Prevention Rather Than Focusing on Treating Symptoms or Advanced Disease

Time and effort spent on prevention often result in a much greater positive impact on outcomes at lower cost because prevention is often more effective in the long run at both the individual and population levels.[27-29] While metformin can delay or prevent the development of type 2 diabetes mellitus, lifestyle interventions are more effective.[30] Tobacco control and smoking cessation efforts (with or without medications) save many more lives than costly chemotherapies for smoking-related cancers.[31]

Use the Test of Time as a Diagnostic and Therapeutic Trial Whenever Possible

Especially when dealing with undiagnosed symptoms or potentially self-limiting conditions, use restraint rather than reflex prescribing to avoid giving drugs that can confuse the clinical picture and compound uncertainties. Reassurance and close follow-up can often be as effective and acceptable to the patient as writing a prescription. Examples of syndromes and diagnoses that have evidence supporting such a delayed strategy include rhinosinusitus,[32] otitis media with effusion,[33] prostate cancer,[34,35] relapsed ovarian cancer,[36] renal masses,[37] back pain,[38] and several hematologic cancers.[39,40]

PRACTICE MORE STRATEGIC PRESCRIBING

Use Only a Few Drugs and Learn to Use Them Well

By becoming familiar with a limited number of drugs, one's knowledge and experience with those medications increases dramatically. By learning in depth how to use a more limited subset of medications and mastering dosing, adverse effects, interactions, and even what the tablets look like,[41] clinicians will be in a better position to prevent errors and anticipate problems. Several European studies have shown that having a more limited personal formulary is associated with higher-quality prescribing, and prescribing drugs with which one is unfamiliar increases the risk of errors.[42-46]

Avoid Frequent Switching to New Drugs Without Clear, Compelling Evidence-Based Reasons

Not only should you have a good reason for starting treatment with a drug, but you should also have a good reason for changing. Have a clear plan with specific parameters and end points to monitor as the basis for decisions about maintaining or modifying therapy.[47] Examples of irrational and often counterproductive medication changes include switching inpatient antibiotics frequently, switching new patients to a physician's favorite medications even though the patient is stable, or changing a regimen that has not had sufficient time to work.[48,49]

Be Skeptical About Individualizing Therapy

While this principle may seem to run counter to the patient-centered care we seek to practice, individualizing therapy can also be a code word for unscientific trial-and-error medicine. Individualization is a mantra of the pharmaceutical industry when it wishes to dismiss disappointing trial results, arguing that they apply only to average patients and not necessarily to the individual patient.[50] The same caution applies to selected patients identified as benefiting in a "subgroup" analysis of an otherwise negative trial.[51,52] Avoid engaging in ad hoc empirical drug trials of your own that, lacking appropriate blinding or failing to account for biases and variations in responses and outcome interpretation, risk producing erroneous conclusions. When it guides precaution (eg, adjusting dose, avoidance in geriatric or hepatic impaired patients, responding to patient response), individualizing can be a plus, but as a license for unscientific experimentation, it needs to be viewed critically.

Whenever Possible, Start Treatment With Only 1 Drug at a Time

Temper the urge to start treatment with medications for a new patient's hypertension, urinary tract infection, dyspepsia, headaches, and toenail infection—all on the first visit. When she develops a rash, or even reports dramatic improvement, you will not know which drug was responsible. While it may be more inconvenient or require multiple visits to start regimens sequentially, it can avoid confusion and give time for more self-limited conditions or ones affected by other problems (eg, headaches improving once blood pressure is lowered) time to resolve on their own.

MAINTAIN HEIGHTENED VIGILANCE REGARDING ADVERSE EFFECTS

Have a High Index of Suspicion for Adverse Drug Effects

Could "fibromyalgia" pain be statin-induced myopathy,[26] worsening heart failure due to an NSAID[53] or rosiglitazone?[54] Become an expert about adverse reactions from drugs you prescribe. Anticipate, ask about, and monitor for common and even rarer but important reactions. No matter how unusual or unlikely a symptom a patient reports, for any problem that develops while a patient is taking a medication, always consider that it might be drug related. Similarly, alert practitioners have discovered many important previously unknown reactions.

Educate Patients About Possible Adverse Effects to Ensure That They Are Recognized as Early as Possible

Physicians often express fears of patients being overly susceptible to symptoms of medication adverse effects when education about those effects is provided. However, these fears have been shown to be exaggerated and are outweighed by the benefit of better-informed patients.[55-58]

Be Alert to Clues That You May Be Treating or Risking Withdrawal Symptoms

There is a long history of drugs being promoted as a cure (eg, heroin as treatment for opium addiction) when they are actually perpetuating the problem. Alcohol is a familiar example, where patients report needing to drink to treat the shakes or insomnia. Caffeine, butalbital, or other analgesics used to treat headaches are now recognized to cause chronic daily headaches via cycles of chronic overuse and withdrawal.[59,60] Proton-pump inhibitors can lead to rebound hyperacidity when given to healthy volunteers.[61] Even for effective medications such as selective serotonin reuptake inhibitors,[62] clonidine,[63] or β-blockers,[64] be cautious in interpreting symptom relapse when a drug treatment is discontinued; these symptoms might actually be withdrawal symptoms.[65]

APPROACH NEW DRUGS AND NEW INDICATIONS CAUTIOUSLY AND SKEPTICALLY

Learn About New Drugs and New Indications From Trustworthy, Unbiased Sources

Avoid education from pharmaceutical representatives or "experts" with conflicts of interest; instead turn to independent drug bulletins (eg, Medical Letter, Prescrire, Worst Pills, Best Pills)[66] or specialists with reputations for integrity and conservative approaches. Evaluate claims for new drugs skeptically, insisting on evidence that they are demonstrably better than existing (drug or nondrug) therapy.

Do Not Rush to Use Newly Marketed Drugs

Even when new drugs are seemingly safer or more effective, experience with them is generally limited; not enough time has elapsed and/or too few patients have been exposed to them for longer-term or rarer adverse effects to be identified.[67-71] Generic, hence older, drugs are generally safer owing to their longer track record. Some have advocated a 7-year rule (ie, wait 7 years before using a new drug), based on data showing that it often takes 5 to 10 years to identify significant adverse effects.[72,73] In premarketing trials, only carefully selected patients are exposed, who, unlike many of our own patients, are often younger and not already taking multiple medications. Thus, there is a paucity of data studying patients like those we typically care for. Our more typical patients, who have multiple medical problems; do not reliably comply with drug regimens; have preexisting renal, liver, or cardiovascular disease; or are already taking multiple other drugs, are often excluded from clinical trials.[74-78]

Be Certain That the Drug Improves Actual Patient-Centered Clinical Outcomes Rather Than Just Treating or Masking a Surrogate Marker

Many well-designed randomized trials show statistically significant improvement in laboratory, radiologic, or other markers of disease risk, severity, or prognosis but may lack proof of a meaningful clinical benefit. Improving these markers may not improve clinical outcomes. There is a growing body of literature demonstrating situations where such surrogate improvements do not translate into clinical benefits (eg, survival, quality of life, complications, mortality) and may even worsen outcomes.[79-84] Historic and more recent examples providing lessons all prescribers should become familiar with include CAST[85] (Cardiac Arrhythmia Suppression Trial) (suppression of premature ventricular contractions increased risk of sudden death); Concorde[86] (improving CD4 counts with zidovudine did not improve survival of patients with human immunodeficiency virus); CHOIR[87] (Correction of Hemoglobin and Outcomes in Renal Insufficiency) and CREATE[88] (Cardiovascular Risk Reduction by Early Treatment With Epoetin) (greater boosting of hemoglobin levels with erythropoietin in dialysis patients worsened outcomes); ENHANCE[89] (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) (ezetimibe combination was more effective in lowering lipids but did not translate into clinical benefit); and ACCORD[90,91] (Action to Control Cardiovascular Risk in Diabetes) (more intensive lowering of hemoglobin A_{1c} levels worsened outcomes in patients with type 2 diabetes mellitus).

Be Vigilant About Indications Creep

Even indications for drugs approved by the US Food and Drug Administration must be viewed with caution: while the drug was shown to be effective for the specific indication studied, those patients or situations might not match your patient. Prescribers need to better understand the precise niche for each drug: *Which* patients with headaches should receive a triptan? *What drugs* should be tried first? *When* is it best to initiate treatment with triptans? Prescribing based on a presumption that your patient or situation is the same as those in published trials and will benefit equally is not evidence-based prescribing; your patient and/or your context might be substantially different. Making bigger leaps to different indications (gabapentin works for postherpetic neuralgia; thus, it is worth trying for migraines) moves further out to an evidence-free zone.[92]

Do Not Be Seduced by Elegant Molecular Pharmacology or Drug Physiology

The notion that the sophisticated molecular structure of a designer drug can reliably predict how that drug will behave in humans has repeatedly led to "nasty surprises."[93(p19)] It is reasonable for industry to pursue such promising basic science leads, but prescribers should await evidence of actual beneficial clinical outcomes and not succumb to theoretical promises of advantage, no matter how compelling. A recent example was the promising drug Torcetrapib (CP-529 414; Pfizer, New York, New York), designed to block cholesteryl ester transfer protein and thereby increase high-density lipoprotein levels, yet 2 large trials showed that it failed to slow atherosclerosis and actually increased mortality.[94,95]

Beware of Selective Reporting of Studies

Widely promoted studies may actually yield a mixture of positive and not so positive findings; and yet often only the positive results are promoted by the sponsor or by enthusiastic investigators.[96,97] Worse yet is the selective publication of trials with positive results, a problem that journal editors have attempted to rectify by requiring advance registration of clinical trials. However, implementation of this oversight system has been imperfect, and prescribers should not feel overly confident that selective publication does not still occur.[97-99] Positive selectivity is even more true for the literature supplied by pharmaceutical sales representatives, which should be assumed to highlight benefits and downplay risks found in a given drug study.

WORK WITH PATIENTS FOR A MORE DELIBERATIVE SHARED AGENDA

Do Not Hastily or Uncritically Succumb to Patient Requests for Drugs, Especially Drugs That They Have Heard Advertised

With the growth of direct-to-consumer advertising, clinicians are under greater pressure from their patients to prescribe advertised drugs.[100,101] We do not want to antagonize our patients, and we often lack sufficient time to thoroughly discuss all the benefits and risks of a given drug with the patient requesting it.[102,103] But rather than taking the path of least resistance, consider the broad effects of writing these questionable prescriptions: besides the costs of violating many of the safety and precautionary principles detailed herein, such prescriptions squander opportunities to educate patients and prepare them to be better-informed drug consumers in the future.

Avoid Mistakenly Prescribing Additional Drugs for Refractory Problems, Failing to Appreciate the Potential for Patient Nonadherence

Do not automatically increase drug doses or add new drugs to a regimen for refractory hypertension without strongly considering nonadherence. Physicians consistently underestimate the extent of this problem,[104,105] as evidenced by studies showing that in most instances of poorly controlled hypertension, patients are not taking their prescribed medications.[106,107]

Avoid Repeating Prescriptions for Drugs That a Patient Has Previously Tried Unsuccessfully or That Caused an Adverse Reaction

It is surprising how frequently a physician will unknowingly prescribe a drug that has previously failed to benefit the patient or that has even caused an adverse reaction due to a lack of an accurate longitudinal medication history. Without a complete drug history (including reasons for starting and stopping treatment with medicines), prescribers risk writing wasteful and potentially harmful prescriptions for drugs that have previously failed.[108]

Discontinue Treatment With Drugs That Are Not Working or Are No Longer Needed

Many conditions or patients are unresponsive to particular drugs. We need to look for such response failures and discontinue treatment with the drug as soon as this is recognized. By identifying patients who are not benefiting, a subset of patients can be spared the expense and adverse effects of continuing treatment with an ineffective medication.[109,110] The timing of such decisions can be difficult because one can always hope that there will be a delayed response, but often this is wishful thinking.[111]

Work With Patients' Desires to Be Conservative With Medications

While some patients appear to want, or even demand, the latest drugs, this stereotype of demanding patients leads physicians to fail to appreciate that there are many others who have the opposite philosophy.[112-114] These more pharmacologically conservative patients are often reluctant to start drug treatments due to real or exaggerated fears or deep personal health beliefs. Work with patients to take advantage of their healthy skepticism, engaging in a dialogue that aligns your own skepticism with theirs via honest education, negotiation, and cautiousness about prescribing. Once you have established your own credibility and earned your patient's trust in your judicious approach to limiting drug therapy to situations where it is truly needed, patients will more readily accept treatment recommendations when medications are truly essential.

CONSIDER LONGER-TERM, BROADER EFFECTS

Think Beyond Short-Term Beneficial Drug Effects to Consider Longer-Term Benefits and Risks

Systemic antifungal agents for onychomycosis[115] or various antiobesity drugs[71,116] can work in the short run but often are not effective in the long term and have relapse rates as high as 50%. Dopamine antagonists such as chlorpromazine and haloperidol, which caused tardive dyskinesias, continue to haunt us as examples of drugs that were dramatically effective but were later found to cause irreversible structural brain damage.[117] Patients given the current generation of allegedly safer antipsychotic medications are now experiencing serious weight gain and increased risks for diabetes as longer-term metabolic effects.[118] Diethylstilbestrol, prescribed for an indication for which it did not even work—preventing miscarriages—was found to cause vaginal cancers a full generation later in daughters who were exposed in utero.[119] Potential longer-term genetic concerns warrant caution.[120,121] Growing resistance to antimicrobial drugs requires consideration of the ecologic impact of every antibiotic prescription or chemical used or discarded into the water supply.[122]

Look for Opportunities to Improve Prescribing Systems, Changes That Can Make Prescribing and Medication Use Safer

Implementing well-designed computerized prescriber order entry or improved patient or laboratory monitoring has been shown to improve drug treatment, often more than the marginal impact of many new "breakthrough" drugs.[123-127] An essential "ingredient" in a successful drug regimen is an informed patient who knows why, when, and how to take a drug and is educated about adverse effects.[128]

CONCLUSIONS

Individually, none of these principles is particularly novel, nor should any of them be terribly controversial. But taken together, they represent a shift in prescribing paradigm from "newer and more is better" to "fewer and more time tested is best."[3(p867)] The recent spate of revelations of undisclosed and unexpected adverse effects of drugs in multiple therapeutic categories[71,129] should serve as wake-up calls for our profession to take a more sober, balanced, and cautious approach to prescribing.[130] Lest these experiences be forgotten, with the resulting failure to draw more general lessons, we urge clinicians to take a more cautious approach to prescribing and administering chemicals whose effects are imperfectly understood. While clinicians must always weigh the benefits of conservative prescribing against the risks of withholding potentially needed medications, at the very least we should seek to shift the burden of proof toward demanding a higher standard of evidence of benefit before exposing patients to the risks of drugs.

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REFERENCES

1. US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. Table 92: selected prescription and nonprescription drugs recorded during physician office visits and hospital outpatient department visits, by sex and age: United States, 1995-1996 and 2003-2004. http://www.cdc.gov/nchs/data/hus/hus06.pdf#092. Accessed April 26, 2011.
2. Sommers JP; US Dept of Health and Human Services, Agency for Healthcare Research and Quality. Statistical brief 158: prescription drug expenditures in the 10 largest states for persons under age 65, 2004. http://www.meps.ahrq.gov/mepsweb/data_files/publications/st158/stat158.shtml. Accessed April 26, 2011.
3. Schiff GD, Galanter WL. Promoting more conservative prescribing. *JAMA*. 2009;301(8):865-867.
4. World Health Organization. Selection and rational use of medications. http://www.who.int/medicines/areas/rational_use/en/index.html. Accessed March 29, 2011.
5. Hamilton HJ, Gallagher PF, O'Mahony D. Inappropriate prescribing and adverse drug events in older people. *BMC Geriatr*. 2009;9(9):5.
6. Rigler SK, Jachna CM, Perera S, Shireman TI, Eng ML. Patterns of potentially inappropriate medication use across three cohorts of older Medicaid recipients. *Ann Pharmacother*. 2005;39(7-8):1175-1181.
7. Zhang Y, Baicker K, Newhouse JP. Geographic variation in Medicare drug spending. *N Engl J Med*. 2010;363(5):405-409.
8. Nugent R, Back E, Beith A. The race against drug resistance: a report of the Center for Global Development's Drug Resistance Working Group. http://www.awmueller.com/deposito/www_cgdev_org.pdf. Accessed April 26, 2010.
9. Krumholz HM, Lee TH. Redefining quality—implications of recent clinical trials. *N Engl J Med*. 2008;358(24):2537-2539.
10. Martizzi M, Tickner J. *The Precautionary Principle: Protecting Public Health, the Environment and the Future of Our Children*. Geneva, Switzerland: World Health Organization Europe; 2004.
11. Myers N. The precautionary principle puts values first. *Bull Sci Technol Soc*. 2002;22(3):210-219.
12. Association of American Medical Colleges. Contemporary issues in medicine: education in safe and effective prescribing practices: July 2008. https://wiki.usask.ca/download/attachments/129138760/Prescribing+Practices.AAMC.pdf?version=1&modificationDate=1257795302000. Accessed April 26, 2011.
13. Garbutt JM, Highstein G, Jeffe DB, Dunagan WC, Fraser VJ. Safe medication prescribing: training and experience of medical students and housestaff at a large teaching hospital. *Acad Med*. 2005;80(6):594-599.
14. Avorn J. *Powerful Medicines: The Benefits, Risks and Costs of Prescription Drugs*. New York, NY: Random House Inc; 2004.
15. Angel M. Big pharma, bad medicine, how corporate dollars corrupt research and education. http://bostonreview.net/BR35.3/angell.php. Accessed March 29, 2011.
16. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.
17. Horvath K, Jeitler K, Siering U, et al. Long-term effects of weight-reducing interventions in hypertensive patients: systematic review and meta-analysis. *Arch Intern Med*. 2008;168(6):571-580.
18. Ratner R, Goldberg R, Haffner S, et al; Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care*. 2005;28(4):888-894.
19. Joshi S. Nonpharmacologic therapy for insomnia in the elderly. *Clin Geriatr Med*. 2008;24(1):107-119, viii.
20. Fiechtner J, Dinning D. Non-pharmacologic treatment options in rheumatologic disease. *Curr Rheumatol Rep*. 2009;5(4):199-203.
21. Lee YC, Shmerling RH. The benefit of nonpharmacologic therapy to treat symptomatic osteoarthritis. *Curr Rheumatol Rep*. 2008;10(1):5-10.
22. Lake AE III. Behavioral and nonpharmacologic treatments of headache. *Med Clin North Am*. 2001;85(4):1055-1075.
23. Kung AW, Pang RW, Janus ED. Elevated serum lipoprotein(a) in subclinical hypothyroidism. *Clin Endocrinol (Oxf)*. 1995;43(4):445-449.
24. Stenson WF, Newberry R, Lorenz R, Baldus C, Civitelli R. Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. *Arch Intern Med*. 2005;165(4):393-399.
25. Huang GD, Feuerstein M, Sauter SL. Occupational stress and work-related upper extremity disorders: concepts and models. *Am J Ind Med*. 2002;41(5):298-314.
26. Buettner C, Davis RB, Leveille SG, Mittleman MA, Mukamal KJ. Prevalence of musculoskeletal pain and statin use. *J Gen Intern Med*. 2008;23(8):1182-1186.
27. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive medications. *Circulation*. 2006;114(2):160-167.
28. Chiuve SE, Rexrode KM, Spiegelman D, Logroscino G, Manson JE, Rimm EB. Primary prevention of stroke by healthy lifestyle. *Circulation*. 2008;118(9):947-954.
29. Hatziandreu EI, Koplan JP, Weinstein MC, Caspersen CJ, Warner KE. A cost-effectiveness analysis of exercise as a health promotion activity. *Am J Public Health*. 1988;78(11):1417-1421.
30. Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med*. 2009;151(5):306-314.
31. Schroeder SA, Warner KE. Don't forget tobacco. *N Engl J Med*. 2010;363(3):201-204.
32. Hwang PH. A 51-year-old woman with acute onset of facial pressure, rhinorrhea, and tooth pain: review of acute rhinosinusitis. *JAMA*. 2009;301(17):1798-1807.
33. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ*. 2001;322(7282):336-342.
34. Arredondo SA, Downs TM, Lubeck DP, et al. Watchful waiting and health related quality of life for patients with localized prostate cancer: data from CaPSURE. *J Urol*. 2008;179(5)(Suppl):S14-S18.
35. Bill-Axelson A, Holmberg L, Ruutu M, et al; Scandinavian Prostate Cancer Group Study No. 4. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2005;352(19):1977-1984.
36. Rustin GJ, van der Burg ME, Griffin CL, et al; MRC OV05; EORTC 55955 investigators. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet*. 2010;376(9747):1155-1163.
37. Mattar K, Jewett MA. Watchful waiting for small renal masses. *Curr Urol Rep*. 2008;9(1):22-25.
38. Shen FH, Samartzis D, Andersson GB. Nonsurgical management of acute and chronic low back

pain. *J Am Acad Orthop Surg*. 2006;14(8):477-487.
39. Ardeshna KM, Smith P, Norton A, et al; British National Lymphoma Investigation. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*. 2003;362(9383):516-522.
40. Portlock CS, Rosenberg SA. No initial therapy for stage III and IV non-Hodgkin's lymphomas of favorable histologic types. *Ann Intern Med*. 1979;90(1):10-13.
41. Schiff GD, Kim S, Seger AC, Bult J, Bates DW. Ability of practitioners to identify solid oral dosage tablets. *Am J Health Syst Pharm*. 2006;63(9):838-843.
42. De Vries TP, Daniels JM, Mulder CW, et al. Should medical students learn to develop a personal formulary? An international, multicentre, randomised controlled study. *Eur J Clin Pharmacol*. 2008;64(6):641-646.
43. Robertson J, Fryer JL, O'Connell DL, Smith AJ, Henry DA. Personal formularies. An index of prescribing quality? *Eur J Clin Pharmacol*. 2001;57(4):333-341.
44. Rucker TD, Schiff G. Drug formularies: myths-in-formation. *Med Care*. 1990;28(10):928-942.
45. Bates DW. A 40-year-old woman who noticed a medication error. *JAMA*. 2001;285(24):3134-3140.
46. de Bakker DH, Coffie DS, Heerdink ER, van Dijk L, Groenewegen PP. Determinants of the range of drugs prescribed in general practice: a cross-sectional analysis. *BMC Health Serv Res*. 2007;7:132.
47. Berwick DM. Controlling variation in health care: a consultation from Walter Shewhart. *Med Care*. 1991;29(12):1212-1225.
48. Edlinger M, Baumgartner S, Eltanaihi-Furtmüller N, Hummer M, Fleischhacker WW. Switching between second-generation antipsychotics: why and how? *CNS Drugs*. 2005;19(1):27-42.
49. Sherr L, Lampe F, Norwood S, et al. Successive switching of antiretroviral therapy is associated with high psychological and physical burden. *Int J STD AIDS*. 2007;18(10):700-704.
50. Parker M. False dichotomies: EBM, clinical freedom, and the art of medicine. *Med Humanit*. 2005;31(1):23-30.
51. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet*. 2000;355(9209):1064-1069.
52. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. *Ann Intern Med*. 1992;116(1):78-84.
53. Mamdani M, Juurlink DN, Lee DS, et al. Cyclooxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet*. 2004;363(9423):1751-1756.
54. Hartung DM, Touchette DR, Bultemeier NC, Haxby DG. Risk of hospitalization for heart failure associated with thiazolidinedione therapy: a medicaid claims-based case-control study. *Pharmacotherapy*. 2005;25(10):1329-1336.
55. Pollock M, Bazaldua OV, Dobbie AE. Appropriate prescribing of medications: an eight-step approach. *Am Fam Physician*. 2007;75(2):231-236.
56. Lamb GC, Green SS, Heron J. Can physicians warn patients of potential side effects without fear of causing those side effects? *Arch Intern Med*. 1994;154(23):2753-2756.
57. Campbell WH, Califf RM. Improving communication of drug risks to prevent patient injury: proceedings of a workshop. *Pharmacoepidemiol Drug Saf*. 2003;12(3):183-194.
58. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol*. 2000;136(3):323-327.
59. Bahra A, Walsh M, Menon S, Goadsby PJ. Does chronic daily headache arise de novo in association with regular use of analgesics? *Headache*. 2003;43(3):179-190.
60. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. *Lancet Neurol*. 2004;3(8):475-483.
61. Reimer C, Søndergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology*. 2009;137(1):80-87, 87, e1.
62. Haddad PM. Antidepressant discontinuation syndromes. *Drug Saf*. 2001;24(3):183-197.
63. Karachalios GN, Charalabopoulos A, Papalimneou V, et al. Withdrawal syndrome following cessation of antihypertensive drug therapy. *Int J Clin Pract*. 2005;59(5):562-570.
64. Miller RR, Olson HG, Amsterdam EA, Mason DT. Propranolol-withdrawal rebound phenomenon. Exacerbation of coronary events after abrupt cessation of antianginal therapy. *N Engl J Med*. 1975;293(9):416-418.
65. Medawar C, Hardon A. *Medicines Out of Control? Antidepressants and the Conspiracy of Goodwill*. Amsterdam, the Netherlands: Aksant; 2004.
66. Olsson S, Pal S. Drug bulletins: independent information for global use. *Lancet*. 2006;368(9539):903-904.
67. Issa AM, Phillips KA, Van Bebber S, et al. Drug withdrawals in the United States: a systematic review of the evidence and analysis of trends. *Curr Drug Saf*. 2007;2(3):177-185.
68. Baron JA, Sandler RS, Bresalier RS, et al. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. *Lancet*. 2008;372(9651):1756-1764.
69. Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. *Arch Intern Med*. 2009;169(19):1737-1739.
70. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. *Arch Intern Med*. 2009;169(19):1756-1761.
71. James WP, Caterson ID, Coutinho W, et al; SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med*. 2010;363(10):905-917.
72. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA*. 2002;287(17):2215-2220.
73. Ross JS, Madigan D, Hill KP, Egilman DS, Wang Y, Krumholz HM. Pooled analysis of rofecoxib placebo-controlled clinical trial data: lessons for postmarket pharmaceutical safety surveillance. *Arch Intern Med*. 2009;169(21):1976-1985.
74. Institute of Medicine. The future of drug safety: action steps for Congress. http://www.iom.edu/~/media/Files/Report%20Files/2006/The-Future-of-Drug-Safety/futureofdrugsafety_reportbrief.pdf. Accessed April 26, 2011.
75. Furberg CD, Levin AA, Gross PA, Shapiro RS, Strom BL. The FDA and drug safety: a proposal for sweeping changes. *Arch Intern Med*. 2006;166(18):1938-1942.
76. Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA*. 1999;281(9):824-829.
77. Fleming TR. Identifying and addressing safety signals in clinical trials. *N Engl J Med*. 2008;359(13):1400-1402.
78. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med*. 2003;349(5):474-485.
79. Fleming TR. Objective response rate as a surrogate end point: a commentary. *J Clin Oncol*. 2005;23(22):4845-4846.
80. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996;125(7):605-613.
81. Konstam MA, Gheorghiade M, Burnett JC Jr, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297(12):1319-1331.
82. Montori VM, Gandhi GY, Guyatt GH. Patient-important outcomes in diabetes—time for consensus. *Lancet*. 2007;370(9593):1104-1106.
83. Psaty BM, Lumley T. Surrogate end points and FDA approval: a tale of 2 lipid-altering drugs. *JAMA*. 2008;299(12):1474-1476.
84. Psaty BM, Weiss NS, Furberg CD, et al. Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease. *JAMA*. 1999;282(8):786-790.
85. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324(12):781-788.
86. Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet*. 1994;343(8902):871-881.
87. Singh AK, Szczech L, Tang KL, et al; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355(20):2085-2098.
88. Drüeke TB, Locatelli F, Clyne N, et al; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355(20):2071-2084.
89. Drazen JM, Jarcho JA, Morrissey S, Curfman GD. Cholesterol lowering and ezetimibe. *N Engl J Med*. 2008;358(14):1507-1508.
90. Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.
91. Nilsson PM. ACCORD and risk-factor control in type 2 diabetes. *N Engl J Med*. 2010;362(17):1628-1630.
92. Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med*. 2006;145(4):284-293.

93. Howard J. Environmental "nasty surprise" as a window on precautionary thinking. *IEEE Technol Soc Mag*. 2003;22(4):19-22.
94. Kastelein JJ, van Leuven SI, Burgess L, et al; RADIANCE 1 Investigators. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med*. 2007; 356(16):1620-1630.
95. Nissen SE, Tardif JC, Nicholls SJ, et al; ILLUSTRATE Investigators. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med*. 2007;356(13): 1304-1316.
96. Wright JM, Perry TL, Bassett KL, Chambers GK. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. *JAMA*. 2001;286(19): 2398-2400.
97. Kyzas PA, Loizou KT, Ioannidis JP. Selective reporting biases in cancer prognostic factor studies. *J Natl Cancer Inst*. 2005;97(14):1043-1055.
98. DeAngelis CD, Drazen JM, Frizelle FA, et al; International Committee of Medical Journal Editors. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *JAMA*. 2004;292(11):1363-1364.
99. Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ*. 2005;330(7494):753.
100. Donohue JM, Cevasco M, Rosenthal MB. A decade of direct-to-consumer advertising of prescription drugs. *N Engl J Med*. 2007;357(7): 673-681.
101. Kravitz RL, Epstein RM, Feldman MD, et al. Influence of patients' requests for direct-to-consumer advertised antidepressants: a randomized controlled trial. *JAMA*. 2005;293 (16):1995-2002.
102. Bell RA, Wilkes MS, Kravitz RL. Advertisement-induced prescription drug requests: patients' anticipated reactions to a physician who refuses. *J Fam Pract*. 1999;48(6):446-452.
103. Paterniti DA, Fancher TL, Cipri CS, Timmermans S, Heritage J, Kravitz RL. Getting to "no": strategies primary care physicians use to deny patient requests. *Arch Intern Med*. 2010;170 (4):381-388.
104. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med*. 2009; 180(9):817-822.
105. Schmittdiel JA, Uratsu CS, Karter AJ, et al. Why don't diabetes patients achieve recommended risk factor targets? Poor adherence versus lack of treatment intensification. *J Gen Intern Med*. 2008;23(5):588-594.
106. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J*. 2008;155 (4):772-779.
107. Ho PM, Magid DJ, Shetterly SM, et al. Importance of therapy intensification and medication nonadherence for blood pressure control in patients with coronary disease. *Arch Intern Med*. 2008;168(3):271-276.
108. Crespin DJ, Modi AV, Wei D, et al. Repeat medication errors in nursing homes: Contributing factors and their association with patient harm. *Am J Geriatr Pharmacother*. 2010;8(3):258-270.
109. Finnerty FA Jr. Step-down therapy in hypertension. Importance in long-term management. *JAMA*. 1981;246(22):2593-2596.
110. Zillich AJ, Shay K, Hyduke B, et al. Quality improvement toward decreasing high-risk medications for older veteran outpatients. *J Am Geriatr Soc*. 2008;56(7):1299-1305.
111. Gawande A. Letting go: what should medicine do when it can't save your life? The New Yorker [August 2, 2010]. http://www.newyorker.com/reporting/2010/08/02/100802fa_fact_gawande. Accessed April 26, 2011.
112. Benson J, Britten N. Patients' decisions about whether or not to take antihypertensive drugs: qualitative study. *BMJ*. 2002;325(7369):873.
113. Phatak HM, Thomas J III. Relationships between beliefs about medications and nonadherence to prescribed chronic medications. *Ann Pharmacother*. 2006;40(10):1737-1742.
114. Hansen DL, Holstein BE, Hansen EH. "I'd rather not take it, but… ": young women's perceptions of medicines. *Qual Health Res*. 2009; 19(6):829-839.
115. Epstein E. How often does oral treatment of toenail onychomycosis produce a disease-free nail? An analysis of published data. *Arch Dermatol*. 1998;134(12):1551-1554.
116. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. *Lancet*. 2007;369(9555):71-77.
117. Remington G. Tardive dyskinesia: eliminated, forgotten, or overshadowed? *Curr Opin Psychiatry*. 2007;20(2):131-137.
118. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999; 156(11):1686-1696.
119. Melnick S, Cole P, Anderson D, Herbst A. Rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix. An update. *N Engl J Med*. 1987;316(9):514-516.
120. Giusti RM, Iwamoto K, Hatch EE. Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med*. 1995;122(10):778-788.
121. Rubin MM. Antenatal exposure to DES: lessons learned . . . future concerns. *Obstet Gynecol Surv*. 2007;62(8):548-555.
122. Jones OA, Voulvoulis N, Lester JN. Potential ecological and human health risks associated with the presence of pharmaceutically active compounds in the aquatic environment. *Crit Rev Toxicol*. 2004;34(4):335-350.
123. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA*. 1998;280(15):1311-1316.
124. Schiff GD, Rucker TD. Computerized prescribing: building the electronic infrastructure for better medication usage. *JAMA*. 1998;279(13): 1024-1029.
125. Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. *Arch Intern Med*. 2003;163(8):893-900.
126. Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. *J Am Med Inform Assoc*. 2008; 15(5):585-600.
127. Baciu A, Stratton K, Burke SP; Committee on the Assessment of the US Drug Safety System. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Atlanta, GA: The National Academies Press; 2007.
128. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-497.
129. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet*. 2005;365(9458):475-481.
130. Giugliano D, Esposito K. Clinical inertia as a clinical safeguard. *JAMA*. 2011;305(15):1591-1592.