

ONLINE FIRST | LESS IS MORE

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 rhinosinusitis,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 wors-

ening heart failure due to an NSAID⁵³ 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, Prescribe, 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 CAST⁸⁵ (Cardiac Arrhythmia Suppression Trial) (suppression of premature ventricular contractions increased risk of sudden death); Concorde⁸⁶ (improving CD4 counts with zidovudine did not improve survival of patients with human immunodeficiency virus); CHOIR⁸⁷ (Correction of Hemoglobin and Outcomes in Renal Insufficiency) and CREATE⁸⁸ (Cardiovascular Risk Reduction by Early Treatment With Epoetin) (greater boosting of hemoglobin levels with erythropoietin in dialysis patients worsened outcomes); ENHANCE⁸⁹ (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 situ-

ations 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 onychomycosis¹¹⁵ or various anti-obesity 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 success-

ful 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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