Principles For Evidence-Based Drug Formulary Policy

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Expenditures for prescription drugs continue to increase, prompting insurers and health systems to adopt formulary or coverage policies restricting the use of more expensive drugs. Those establishing formulary policies face a complex array of claims regarding differences in efficacy, safety, treatment cost, or cost-effectiveness. We describe and illustrate 5 specific principles for applying research evidence to formulary decisions: (1) Experimental data should take precedence over models or simulations, and assumptions of such models should be carefully examined. (2) Morbidity or mortality outcomes should take precedence over surrogate or intermediate outcomes. (3) Claims for advantages of new treatments should consider the full range of alternatives rather than those selected by industry. (4) Variation in effects across individuals or subgroups argue against restrictions on first-line treatment, but only if those differences are predictable. (5) Variation in effects argues against requiring changes in ongoing treatment. We also discuss how economic incentives are likely to influence selection of research questions, especially research related to drug-gene interactions and to identifying new indications for existing drugs.

KEY WORDS: formulary; drug coverage; economics; cost-effectiveness; pharmacoeconomics.

DOI: 10.1111/j.1525-1497.2005.0232.x

J GEN INTERN MED 2005; 20:964-968.

Between 1997 and 2002, total U.S. expenditures for prescription drugs increased by 115% compared to a 42% increase for all health services expenditures.¹ Prescription drug costs accounted for over 10% of all health expenditures in 2001 compared to less than 7% in 1997.¹ Much of this increase reflects development of new drugs,² most often additions to an existing class of drugs rather than truly novel treatments. Of 1,099 new drug applications approved by the U.S. Food and Drug Administration (FDA) between 1990 and 2002, only 167 (16%) were classified by the FDA as new molecular entities offering significant improvement in treatment, diagnosis, or prevention compared to already marketed products.^{3,4} Direct-to-consumer advertising may further increase demand for expensive branded medications.^{5,6} Faced with increasing costs, health insurers and health care systems have adopted a variety of strategies to contain drug expenditures including greater cost sharing by consumers and restricted formularies for prescribers.

Formulary restrictions^{7,8} and cost-sharing strategies such as tiered copayments⁹ can reduce drug expenditures. These policies, however, have raised concerns among health

care providers and consumers regarding reduced adherence to ongoing care¹⁰ and restricted access to new treatments.¹¹⁻¹⁴ The American Medical Association (AMA) and others have questioned the ethics of formulary restrictions based solely on price.^{11,15} In 2000, the AMA, the National Business Coalition on Health, and other national health care organizations published *Principles of a Sound Drug Formulary System*.¹⁶ These principles state that cost factors should be considered only after safety, efficacy, and therapeutic need and that treatments should be evaluated in terms of impact on total health care costs. The Academy of Managed Care Pharmacy has proposed a standard format to describe and evaluate the benefits and costs of new drug treatments.^{17,18}

Recent legislation establishing a Medicare prescription drug program authorized the use of restricted formularies and higher copayments for more expensive drugs. The legislation states that final coverage decisions be based on medical necessity and that formularies must include at least 2 drugs in each therapeutic category and drug class. Model guidelines proposed by the U.S. Pharmacopeia specify 146 therapeutic classes (e.g., a single class for all sedative-hypnotic drugs and a single class for all nonsteroidal anti-inflammatory drugs).

A formulary committee attempting to define medical necessity cannot be expected to conduct independent research. Instead, decision makers must interpret a complex array of claims regarding efficacy, safety, adverse effects, and treatment cost or cost-effectiveness. Arguments for coverage of new drug treatments are often supported by industry-funded analyses and by advocacy groups with strong industry ties. Garber¹⁹ has described guidelines for evidence-based coverage decisions regarding novel procedures or technologies. Formulary decisions more often consider several drugs approved for the same indication or clinical condition. We propose here 5 principles that formulary committees might use to isolate critical questions and identify relevant evidence.

EXPERIMENTAL DATA VERSUS MODELS OR SIMULATIONS

In comparing benefits, risks, and costs of alternative treatments, evidence from true experiments or randomized controlled trials should certainly be given greatest weight. Typical clinical trials, however, assess short-term efficacy in selected populations. Randomized trials to examine long-term safety, effectiveness, and cost-effectiveness are large, long, and expensive. When adequate experimental data are not available, policy-makers must sometimes rely on decision-analytic

Dr. Psaty has provided expert testimony regarding safety of antihypertensive drugs. Dr. Simon has received research grants from Eli Lilly & Co., Solvay Pharmaceuticals, and Pfizer Pharmaceuticals.

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Received for publication January 4, 2005

and in revised form May 17, 2005

Accepted for publication June 22, 2005

models to simulate comparisons between alternative treatments. Those models often depend on expert opinion for critical inputs. Selected results from short-term trials in selected populations are often extrapolated to long term or to more heterogeneous populations. Opportunities for bias are frequent, and models can sometimes be used to simulate clinical or economic benefits that cannot be replicated in randomized trials. When models or simulations are the best data available, appropriate skepticism is necessary. Formulary committees should certainly compare model results to available experimental data and examine the sensitivity of results to key assumptions. Proprietary models dependent on hidden assumptions should be suspect.

Examples

Several cost-effectiveness models (often industry-supported) have argued for first-line use of cyclooxygenase-2 (Cox-2) inhibitor drugs for the treatment of arthritis.^{20,21} These models typically presume that Cox-2 inhibitors and older anti-inflammatory drugs have equal efficacy, but they claim cost savings or superior cost-effectiveness for newer drugs because of fewer severe gastrointestinal events. The assumption that use of Cox-2 inhibitors significantly reduces long-term rates of serious gastrointestinal events has not been consistently demonstrated in randomized trials,^{22–25} and recent data suggest increased risk of cardiovascular events.^{26–28} It appears that such models were based on the most optimistic assumptions regarding benefit and risk.

Several cost-effectiveness models of donepezil treatment for Alzheimer's disease^{29,30} have extrapolated from short-term clinical results to predict lower rates of institutionalization and reduced costs of care. The only long-term trial evaluating these economic outcomes found no benefit over placebo.³¹

SURROGATE OR INTERMEDIATE OUTCOMES

Drugs prescribed for disease prevention or risk factor reduction are sometimes approved and marketed based on changes in surrogate end points such as reduction in blood pressure or lipid levels. Changes in risk factors or surrogate outcomes do not necessarily translate to actual health benefit, and 2 treatments with equivalent effects on a surrogate outcome may not have equivalent effects on outcomes that matter.³² Evidence of reduced morbidity or mortality should carry greater weight than evidence based solely on surrogate end points.

Example

During the 1980s encainide and flecainide were approved for treatment of ventricular arrhythmia on the basis of evidence that both drugs suppressed ventricular ectopic contractions (the intermediate outcome). A subsequent randomized trial³³ demonstrated that compared to placebo, these drugs actually increased the risk of cardiovascular mortality and mortality caused by arrhythmia (the important health outcomes).

CONSIDERING THE FULL RANGE OF COMPARISONS

The clinical trials required for regulatory approval of a new product often include comparisons with placebo and at least 1 treatment of known effectiveness. When several treatments are approved for a condition or indication, the randomized trial

evidence base usually includes many, but not all of the possible comparisons. For example several new treatments may be compared to placebo, but not to each other. Simple indirect comparisons (e.g., using separate studies comparing 2 new treatments to placebo in order to infer a comparison between the 2 new treatments) may provide useful observational information.³⁴ Such comparisons, however, will not be valid if populations or procedures differ among studies. When adequate data are available, the technique of network meta-analysis³⁵ evaluates the consistency and validity of direct and indirect comparisons through a form of triangulation (e.g., 2 new treatments can be compared if both have been compared to a third treatment and all 3 have been compared to placebo).

Indirect comparisons are especially important when the comparisons most interesting to clinicians and policy-makers differ from those that are most interesting or advantageous to research sponsors. Network meta-analyses may also help overcome biases caused by comparisons of new drugs with sub-optimal alternative treatments (e.g., higher dose of newer treatment compared to lower dose of standard treatment). Most formulary committees cannot be expected to perform these analyses. Committees or policy makers can, however, request that claims for new drugs explicitly consider the full range of comparator treatments, either through direct comparison or some appropriate form of indirect comparison.

Example

Options for first-line treatment of hypertension include several drug classes (diuretics, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) that differ widely in cost. Over 40 randomized trials have compared 1 or more of these drugs, with some including comparisons to placebo. While these numerous individual comparisons do not clearly indicate a preferred option, a network meta-analysis combining these data³⁶ found that low-dose diuretics (the least expensive treatment) were superior to all other drug classes across a range of cardiovascular outcomes.

VARIATION ACROSS SUBGROUPS OR INDIVIDUALS

Drugs approved for the same indication often show equal efficacy on average despite considerable variability in clinical effects across individual patients or subgroups. This scenario (equal effects on average, significant variability between individuals) can be misinterpreted to support either unnecessarily broad or inappropriately restrictive formulary policies. In the former case, evidence for variation in clinical effects is used to argue that all or most alternatives should be available for first-line treatment. This argument is only reasonable if the patients or subgroups responding preferentially to a more expensive treatment are identifiable at initiation of treatment. If differential response is not predictable, then treatment selection should depend on average effects. If alternative treatments are equal on average, then restricting first-line treatment to the least expensive alternative is well justified. Conversely, evidence of equal effects on average can be misused to argue against allowing more expensive alternatives under any circumstances. Equal efficacy on average does not imply equal efficacy for individual patients, and use of a more expensive

medication is often justified for those responding poorly to first-line treatment.

Example

Direct randomized comparisons of serotonin reuptake inhibitor antidepressants consistently find no difference in average effectiveness for treatment of depression.^{37,38} Cross-over studies, however, demonstrate that half of patients failing to respond to 1 drug in this class may respond well to another.^{39,40} This heterogeneity of response, however, is not predicted by any clinical characteristics at time of starting treatment.³⁷ Rational formulary policy, therefore, might restrict first-line treatment to the least expensive drug in this class while fully covering more expensive options for those not responding to first-line treatment.⁴¹

NEW VERSUS CONTINUING TREATMENT

For conditions requiring long-term treatment, the bulk of drug expenditures are for ongoing therapy rather than new prescriptions. A decision to change formulary policy may have little impact on costs unless it also requires changes in ongoing care, a policy known as therapeutic interchange. Even if alternative drugs produce equal effects on average, requiring patients to switch between treatments may or may not be reasonable. The relevant principle again is that equal effect on average does not necessarily imply equal effect for any individual. As variability in effects, either therapeutic or adverse effects, increases, the risk of harm from therapeutic interchange increases as well. In addition to concerns about variability in effect, decisions regarding therapeutic substitution must also consider added visits and other costs of medication changes as well as the likelihood that many physicians and patients may be hesitant to disrupt stable treatment.

Examples

For drug classes with relatively homogeneous effects such as estrogens⁴² and statins,⁴³ therapeutic interchange may significantly reduce costs without disrupting care sacrificing clinical benefit. In contrast, antidepressant^{39,40} and antipsychotic^{44,45} drugs show significant heterogeneity. Therapeutic interchange within these drug classes would require significant clinical effort and could cause harm to significant numbers of patients.

ECONOMIC INFLUENCES ON THE RESEARCH AGENDA

The principles discussed above are intended to guide formulary committees and other policymakers in applying available evidence to formulary or coverage decisions. Formulary committees must also recall that academic and economic incentives can influence the how evidence is produced and disseminated. Funding incentives may favor publication of data favorable to newer products while unfavorable data remain unpublished.^{46–49} Economic incentives may have even greater influence further upstream in the research process when research questions are identified or selected. Two examples are especially relevant to the current clinical research environment: identifying new indications for existing drugs and discovery of drug-gene interactions.

Economic incentives certainly influence research regarding new indications for existing drug treatments. Several antidepressant drugs, for instance, have recently been approved for the treatment of various anxiety disorders.^{50–52} Given the effort and expense required for approval by the Food and Drug Administration, applications for new indications will usually be limited to more expensive branded drugs. When only the more expensive drug or drugs in a class are approved for a new indication, policymakers must consider whether evidence also supports use of similar but less expensive alternatives.⁵³ For example, does evidence supporting use of more expensive sustained-release bupropion to aid smoking cessation also support the use of the regular-release product? In some cases, such as use of antidepressants for generalized anxiety, new indications overlap significantly with older ones so that the new indication may not identify a truly distinct population. Consequently, formulary decision makers must consider whether a new indication represents a distinct clinical entity requiring different treatment or simply a largely overlapping indication intended primarily for marketing advantage—a phenomenon called pseudospecificity.⁵⁴

Economic incentives are also likely to influence priorities for pharmacogenetic research. Discovery of drug-gene interactions will probably identify many new examples of predictable heterogeneity in treatment efficacy or safety.⁵⁵ If a particular genotype predicts greater efficacy or fewer adverse events with a specific drug, then a rational formulary policy should consider this clinical benefit and balance greater benefit against increased cost for that subgroup of patients. Industry-sponsored research on drug-gene interactions, however, is likely to focus on more expensive treatments.^{55,56} If a particular genetic polymorphism predicts greater efficacy for 1 member of a drug class, can we extrapolate this finding to other less expensive agents within the same class? Genotypic predictors of superior response to less expensive generic drugs may remain undiscovered.

SUMMARY AND CONCLUSIONS

We describe here 5 principles for applying clinical evidence to formulary policy decisions. (1) Experimental data should take precedence over models or simulations, and assumptions of such models should be carefully examined. (2) Morbidity or mortality outcomes should take precedence over surrogate or intermediate outcomes. (3) Claims for advantages of new treatments should consider the full range of alternatives rather than those selected by industry. (4) Variation in effects across individuals or subgroups argue against restrictions on first-line treatment, but only if those differences are predictable. (5) Variation in effects argues against requiring changes in ongoing treatment. We also discuss how economic incentives are likely to influence selection of research questions, especially research related to new indications and to drug-gene interactions.

Advocates of more expensive treatments sometimes argue that formulary restrictions constitute rationing—a denial of necessary or effective treatment based solely on cost. We argue that evidence-based formulary policies are actually a critical tool for correcting imperfections in the market for prescription drugs.⁵⁷ The current prescription drug market suffers from significant information asymmetry. Consumers of prescription drugs typically lack the information to determine whether

more expensive treatments offer any significant advantage. Producers have strong economic incentives to claim advantages for more expensive drugs. Ideally, a formulary committee acts on behalf of its consumers or constituents to correct this asymmetry and identify new treatments that offer significant benefit. While rationing carries negative connotations, the current prescription drug marketplace often suffers from irrationaling, the allocation of resources with no systematic consideration of effectiveness or value.

When resources are limited, difficult choices are necessary. The principles described here are intended to assist formulary decision makers in applying evidence to those difficult choices. In addition, these principles should give academic and industry researchers a perspective on the type of evidence most relevant to rational drug coverage decisions.

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