How Can Cost-Effectiveness Information Help Control Unsustainable Growth in U.S. Health Care Spending?

TO THE EDITOR: Garber (1) and Wilensky (2) both recognize the importance of information about comparative effectiveness and cost in making rational choices among alternative therapies. Extending Garber’s analogy, without information about comparative effectiveness and cost-effectiveness, we are ordering not only from a menu without prices but also, for many, from a menu written in a foreign language. Both components from a trusted source are needed to make rational, effective health care decisions.

Although we recognize Wilensky’s superb knowledge of political realities, we disagree strongly with her call for a separate entity (that is, the payers) to develop unbiased data on cost-effectiveness. Studies of comparative effectiveness and cost-effectiveness are commonly done together (as in the United Kingdom’s National Institute for Health and Clinical Excellence program), whether within a clinical trial or in analyses of data from combinations of trials. Requiring investigators to seek funding from 2 different entities would impede progress. Furthermore, leaving cost-effectiveness analyses to the payers, as Wilensky suggests, also would bring into question the trustworthiness of the results. Payers have their own interests and perspectives and do not always provide unbiased, transparent analyses.

Although there is clearly a difference of opinion as to whether the production of comparative effectiveness and cost-effectiveness information should lie within the scope of a single entity or more than one, this disagreement should in no way weaken the College’s position that cost is important, that its use must be transparent, and that cost should never be compared without simultaneously considering comparative clinical effectiveness.

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References

TO THE EDITOR: It is admittedly time for the nation to openly discuss cost-effectiveness in health care; therefore, the proposals from Garber (1) and Wilensky (2) are timely. Being a solo practitioner, I view this type of “top-down” policy as similar to some of the previous mandates that may have led us to this situation.

Although I agree with most of the principles in theory, I have reservations about how these might affect community-based clinical practice. First, if such a program is ever implemented, every practice will have to rework every insurance contract that each physician currently has, leading to substantial (un-funded) expenses, which hurt small practices the most. Physicians may just opt out of participating in insurance plans or Medicare if they are mandated to rework these contracts.

Second, if such a cost-effectiveness policy has to be implemented in clinical practice, the current practice of prior authorizations or preapprovals has to be eliminated. The basic premise that a nonclinician working for an insurance company, Medicare, or Medicaid can override a clinical decision made by a physician after a thoughtful clinical evaluation must be eliminated.

Third, although it is fine for a federal agency to initiate the process, state-based subsidiaries must be created to set cost-effectiveness standards based on local issues, such as population characteristics, average education level and types of employment, and even local weather patterns. For example, reimbursement for language translators may be highly cost-effective in certain neighborhoods, whereas provision of transportation may be cost-effective in others. Only people with knowledge of local conditions will be able to decide what is most cost-effective—national agencies will not.

Fourth, before such a program is implemented, physicians have to be provided with legal immunity against litigation, in case of less-than-favorable outcomes related to use of a particular cost-effectiveness program. Without such protection, physicians are highly unlikely to discuss cost-effectiveness issues with a patient. It is vitally important for the authors to remember that the primary intent of a clinical decision is almost always to benefit a patient. The general public also expects no less from their physicians. Adding a cost variable to this equation will most likely erode the strength in the physician–patient relationship, which has already reached a low point. Therefore, this effort has a better chance of success if it starts at the community level and works toward the provider level.

Fifth, with respect to technical details about “cost” and “effectiveness,” it must be clearly stated that “cost” is “allowable cost” and not “billed cost.” Similarly, effectiveness must be disease-specific and not episode-related. For example, it may cost more up front to use a newer medication, but over time, it may save in terms of avoiding all the adverse effects attributable to a comparable older agent. Similarly, it may be expensive to reimburse for disease-specific patient coaching, but it may prove cost-effective in the long term if this prevents recurrent hospital visits. So, the devil is in the details.

Finally, one would expect an organization representing physicians (the American College of Physicians) to make a clear distinction between “explosion of health care costs” and health insurance costs. As a practicing physician who has seen incomes stagnate over the past 10 years despite a marked increase in workload, I refuse to accept that “explosion of health care costs” justifies the use of cost-effectiveness measures, because it legitimizes the notion that cost increases are a direct result of overutilization of ineffective care. In my opinion, the College would serve a greater purpose if researchers could analyze what percentage of increases in insurance premiums has translated into increased payments for health care and what percentage has percolated into the coffers of insurance companies.
I applaud this effort from the College but would like specifics to be added in the future.

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References

TO THE EDITOR: We read with interest the position paper on a national comparative effectiveness program (1) and the related editorials (2, 3). This is very timely because there is general agreement that the growth in health care spending in the United States is unsustainable. We contend that one of the most increasingly important contributors to rising costs is innovations with marginal benefits, and the only way to assess the benefit–financial risk ratio of these marginal benefits is precisely to tie cost-effectiveness with clinical effectiveness. This is best demonstrated with an example.

In 1996, the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study (4) showed the clinical effectiveness of clopidogrel over aspirin, demonstrating an 8.7% relative reduction in recurrent stroke, peripheral vascular disease, and myocardial infarction. If clinical effectiveness and cost-effectiveness considerations were divorced from each other, as suggested by Wilensky (3), there would be no further discussion. However, the reported reduction in recurrent events from 5.8% to 5.3% per year is an improvement in the prevention success rate from 94.2% per year with aspirin to 94.7% with clopidogrel—a marginal improvement that will probably be common with future innovations because our health care system has achieved great baseline success in many areas.

Furthermore, a cost-effectiveness measure is essential in this example, both individually and collectively, because clopidogrel costs about $1560 per year, versus $15 per year for aspirin. Individually, the proposed incremental cost-effectiveness ratio would be $309 000 per event prevented. Collectively, the annual prevalence of the 3 target diseases in 2001, shortly after CAPRIE was published, was 25.8 million people (5). Assuming about 15% of them have a dual diagnosis, that leaves 22 million different individuals. Treating all of them with clopidogrel would have cost $34 billion per year more than treatment with aspirin alone, which would have accounted for 28% of all U.S. pharmaceutical costs and 2.5% of all U.S. health care costs (6) at that time, for that 1 innovation to improve success from 94.2% to 94.7%.

This kind of information is critical if physicians, patients, payers, and policymakers are to make rational decisions to stem the out-of-control health care expenditures that threaten our health and our economy. In this era of numerous marginally beneficial innovations with variable cost increments, the entity proposed by the American College of Physicians is crucial to provide information we all need.

Empirical Use of Fluconazole in Critically Ill Patients: Good Study, but What Was the Hold-up?

TO THE EDITOR: I would like to thank Schuster and colleagues (1) for the excellent article on the empirical use of fluconazole in critically ill patients at high risk for disseminated candidiasis. Their investigation provides valuable data to a broad array of clinicians and addresses an important but understudied area of biomedical research. However, I was troubled to see that, whereas the study was published in 2008, the last patient was enrolled in 1999 and follow-up was completed in 2000 (1). This leads me to ask: What led to an 8-year delay in publication of such critical data? Given that the study was financed and monitored, and the database analyzed, by Pfizer (New York, New York), I was immediately concerned that the funding source may have hindered publication of data that were likely to decrease utilization of a high-impact pharmaceutical. The fact that fluconazole remained under patent from 2000 until 2004, when it became available in generic form, further raises concern over the timing of publication (2). I sincerely hope that there is another, more innocuous explanation for the long delay between closure of the study and publication of the data. Whatever the case may be, I would be interested in any advice the authors might have for how to minimize delay in the dissemination of clinically relevant data in the future. Finally, I ask why neither the editors of Annals of Internal Medicine nor the author of the accompanying editorial (3) addressed the issue of publication delay. Have such practices become so commonplace that they are not worth mentioning?

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Potential Financial Conflicts of Interest: None disclosed.

References
TO THE EDITORS: I was delighted to read the article by Schuster and colleagues (1) on the empirical use of fluconazole in critically ill patients in the intensive care unit (ICU). Although there was an 8-year delay between the completion and publication of the study, it is an excellent example of how a “negative” study still provides valuable data on making empirical antifungal treatment decisions in critically ill patients in the ICU. However, one needs to consider this 8-year gap and place it in the context of practicing medicine in 2008. First, I disagree with the authors’ statement that “yield of Candida species in blood culture is suboptimal even with current culture techniques.” Recently, the ability of automated blood culture systems to recover Candida species has improved. In the simulated candidemia study by Horvath and colleagues (2), Candida species were isolated in 98% (211 of 216) of aerobic blood culture bottles but were detected in only 27% (58 of 216) of anaerobic bottles; this was not unexpected because Candida species are aerobic organisms. Most Candida species were detected within 24 to 48 hours in the automated blood culture system, except for Candida glabrata, which took longer and was detected earlier in anaerobic bottles. Although the yield was not 100%, the study demonstrated the improved ability of current technology to detect candidemia in aerobic cultures. Second, the shift from C. albicans to non-albicans Candida species, such as C. glabrata, as a cause of candidemia is well known (3). Now, the echinocandin class of antifungal drugs is available and covers fluconazole-resistant species. This may be an option for empirical treatment instead of high-dose fluconazole for patients at high risk for candidemia.

On a separate point, the interim analysis needs clarification. At the beginning of the study, the target sample size was 134 participants in each group, with a total of 268 participants. However, the authors stated that after the interim analysis, further enrollment was closed because of lack of a difference in the 2 treatment groups. Of interest, a total of 270 ICU participants were enrolled, which approximates the size of the initial enrollment goal of the study.

The wait for publication was long and the study has some limitations, but it demonstrates the importance of publishing results—whether positive or negative—in a timely manner.

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References

IN RESPONSE: We appreciate the readers’ interest in our study. Dr. Shelburne and Dr. Lee bring up the very important issue of publication delay. Some of the delays that occurred in the reporting of this trial—and in other, similarly complex, multicentered clinical trials conducted in critically ill patient populations—are invariably due to the difficulties in completing the data set after the final patient is enrolled. Performance of quality assurance, data cleaning, site answers to data queries, and review of each individual case by a busy data review committee can be cumbersome and time-intensive processes, which clearly took too long in our study. A study such as ours is a joint venture between the investigators and the sponsor. Although there was an element of initial disappointment with a trial yielding negative results and although the focus of many involved may have been diverted at times during the long process, there was no intentional delay in the publication of these results. Efforts to improve the speed of publication and promote the publication of important clinical trials with negative findings are critical to the dissemination of data that may affect clinical practice. Policies that may speed the publication of clinical trial results include the assignment of dedicated clinical monitors to each study site and the formation of a publication committee and timeline at the onset of the project. In September 2004, an editorial published by the International Committee of Medical Journal Editors (1) stated that, beginning in September 2005, clinical trials could only be considered for publication if they had been publicly registered before patient enrollment. This policy will help promote the reporting of all clinical trials.

With regard to the current yield of routine blood cultures for the growth of Candida species, although the rate of false-negative results for the detection of candidemia is lessened with current blood culture systems, the high attributable mortality rate due to candidemia still makes empirical or prophylactic therapy attractive. Dr. Lee notes correctly that there has been a shift from C. albicans to non-albicans species, including C. glabrata, and that echinocandins may have activity against fluconazole-resistant isolates. Given the substantially higher cost of echinocandins, and the fact that most Candida species remain susceptible to fluconazole (2), it remains to be seen whether empirical therapy with an echinocandin will be beneficial and cost-effective. Dr. Lee also questions the large number of patients enrolled in the trial despite the fact that the trial was terminated at the interim analysis for lack of efficacy. The interim analysis looked at completed patients, and enrollment was not paused but was rapid and ongoing at the time of the analysis. Patients already in the trial at the time of the decision were allowed to complete the study, and thus, 270 patients were ultimately enrolled.

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References
Do Race and Ethnicity Play a Substantial Role in the Quality of Care That Patients Receive in the U.S. Health Care System?

TO THE EDITOR: Sloan (1) describes his patient Amanda Gonzalez and her struggle with a devastating illness, an unjust health care system, and medical error. Her story is tragic. Furthermore, the author speaks of bias in the care she received. Instead of prejudice, this story demonstrates a failing system as a cause of the patient’s delays in care. Like the orthopedist and emergency department physician in Sloan’s story, many others are trying to serve those with the greatest need. We are the physicians working on the front lines of a broken system. Individual racism certainly exists, but systems issues contribute to an overburdened system. These issues pose the greatest challenge to such patients as Amanda Gonzalez. As I consider the orthopedist in the story, I sympathize with a frustrated and busy surgeon. She would have rather not been scheduling underinsured patients 9 months out, I’m certain. Attributing the delay to personal prejudice is unfounded. I would instead attribute it to a fundamentally broken system that further marginalizes the poor.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

INTERNET-ENABLED THYROID HORMONE ABUSE

Background: Patients increasingly use the Internet for health information and services, including the convenient purchase and delivery of prescription drugs.

Objective: To present a case of life-threatening thyroid hormone abuse, encouraged and enabled by unconventional health advice and nonprescribed medication obtained via the Internet.

Case Report: A 56-year-old woman presented to the emergency department with dyspnea and palpitations. Eight years earlier, she underwent thyroidectomy for hyperthyroidism. After thyroidectomy, she took 1-thyroxine but struggled with fatigue and weight gain. She saw 5 endocrinologists and tried various regimens but continued to feel weak and “not herself.” She lost her job, got divorced, and became depressed; fluoxetine did not help her symptoms.

A patient-directed Web site called Stop the Thyroid Madness (1) convinced her to take Armour Thyroid (desiccated porcine thyroxine [T4] and triiodothyronine [T3]; Forest Laboratories, New York, New York) in doses high enough to maintain an undetectable thyroid-stimulating hormone (TSH) level. She was unable to find a

IN RESPONSE: As Dr. Hegedus points out, our health care system is indeed broken. With more than 40 million U.S. residents lacking health insurance, one could hardly argue that point. However, although all U.S. residents are subject to the same broken system, several studies demonstrate that minorities have worse health outcomes. The Institute of Medicine (1) notes that in most studies, differences in care are present even after controlling for other confounding factors. There is ample evidence of racial and ethnic differences in cardiac care (2), cancer care (3), and diabetes (4). Perhaps more important, many physicians erroneously believe that race or ethnicity does not play a substantial role in the quality of care patients receive (2).

Certainly, we cannot know for certain the true feelings or biases (if any) of Amanda Gonzalez’s physicians. We can only know that she, like many nonwhite patients, received substandard care. The literature provides ample evidence of prejudice in U.S. health care. The data do not support ascribing poor outcomes to a “broken system” and dismissing racial and ethnic bias as a cause of poor health outcomes.

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References
doctor willing to support this strategy, so after her last endocrinologist "fired" her, she managed her illness on her own. No domestic pharmacy would supply her with the medication without a prescription, but she eventually obtained the drug illegally from Web sites in Canada and Mexico. For several months, she maintained a regimen of iodine supplements plus Armour Thyroid, 6 grains daily (228 μg T₄ and 54 μg T₃)—twice the manufacturer’s recommended maximum dose for hypothyroidism, and for a while she felt better than she had with any other regimen.

In the emergency department, she had rapid atrial fibrillation and pulmonary and peripheral edema. Total T₄ level was 178.9 nmol/L [13.9 μg/dL] (range, 69.9 to 150.1 nmol/L [5.41 to 11.66 μg/dL]), total T₃ level was 2.5 nmol/L (range, 1.4 to 2.6 nmol/L), and TSH level was less than 0.04 mU/mL (range, 0.32 to 4.05 mU/mL). After treatment with propranolol and furosemide, she converted to sinus rhythm and her congestion resolved. However, echocardiography revealed global left ventricular dysfunction with ejection fraction of 0.20 to 0.25, consistent with thyrotoxic cardiomyopathy. She declined inpatient psychiatric consultation and was discharged with cardiac medication plus Armour Thyroid, 1 grain daily, pending follow-up by a new internist. She felt relieved to get the drug legally but remained frustrated, saying, “No one seems to care what I feel like—they only care about the labs.”

Discussion: Some patients with hypothyroidism have persistent malaise despite biochemically adequate doses of L-thyroxine, but most authorities discourage supraphysiologic dosing, and none endorse more than mild suppression of TSH levels (>0.1 mU/mL) in selected patients (2). Lower levels of TSH have been linked to atrial arrhythmias, cardiac dysfunction, and bone loss and may increase mortality (3).

Announcing “a patient revolution against decades of inferior thyroid treatment,” the Stop the Thyroid Madness Web site instructs patients to take a minimum of 3 to 5 grains daily to eliminate “obvious” hypothyroid symptoms, “even if the TSH is zero” (1). Unfortunately, it provides no caution that malaise might relate to a nonthyroid illness; it advises readers to ignore toxic signs, including tachycardia during treatment; and it maligns physicians who follow evidence-based guidelines for “failing to serve the patient.” Thyroid hormone abuse has been described (4), but such aggressive online promotion heightens our concern.

In the Internet era, physicians can expect to see more cases of self-treatment gone awry. Adverse events are thought to be underreported, but overdoses from narcotic analgesics obtained online by young people have recently gained attention (5, 6). In the United States, it is illegal to dispense medication without authorization by a licensed practitioner and, because of domestic law enforcement, most “rogue” online pharmacies have moved overseas. Agencies are working with Internet service providers and credit card companies to warn consumers, block Web sites, and restrict payments to rogue pharmacies, but loopholes remain (5, 6). Additional measures are needed to protect the public, and clinicians might consider how to better support frustrated patients who may otherwise turn to unproven and possibly unsafe remedies.

Conclusion: Unregulated Internet health information and self-medication via rogue Internet pharmacies contributed to thyrotoxicosis in this patient. This case was reported to Forest Pharmaceuticals and the U.S. Food and Drug Administration.

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References

Heterologous Fat Transplantation for the Treatment of HIV-Related Facial Lipoatrophy

Background: Clinical features of HIV-1–related lipodystrophy prominently include facial lipoatrophy. These abnormalities can adversely affect the psychological well-being of HIV-infected individuals, affecting adherence to antiretroviral drug regimens, body self-image, and overall quality of life (1, 2).

Objective: To evaluate heterologous fat transplant to treat facial lipoatrophy in a set of HIV-serodiscordant homozygous twins and discuss its possible pathogenetic implications.

Case Report: We transplanted abdominal subcutaneous fat from twin 1, the HIV-seronegative donor, to the subcutaneous cheek region of twin 2, the HIV-infected recipient, by using the Coleman technique (3). Twin 2 had been HIV-infected for 18 years and was extensively treated with all 3 major classes of antiretrovirals, notably including stavudine for 50 months. Neither twin was obese (body mass index was 19 kg/m² for twin 1 and 16 kg/m² for twin 2). The local institutional review board authorized the procedure.

Both patients underwent standard pre–solid organ transplantation assessments. We assessed fat graft condition at 14 months after transplantation by using ultrasonographic measurement of dermal and subcutaneous thickness in the Bichat fat pad region, photographic comparisons, and visual analogue scale measurements of patient satisfaction.

During follow-up, there was no change in antiretroviral therapy. The Figure shows the facial appearance of the twins before surgery (Figure, A), 1 day after surgery (Figure, B), and 14 months after surgery (Figure, C). Ultrasonography–measured dermal and subcutaneous thickness of twin 2 (the recipient) demonstrated pretransplantation dermal and subcutaneous measurements of 0.8 mm and 1.5 mm, respectively. Fourteen months after transplantation, dermal and...
subcutaneous thicknesses were 1.7 and 5.8 mm, respectively. Twin 2 was very satisfied with her facial appearance (visual analogue scale score from before to 14 months after transplantation improved from 1 to 10).

Discussion: This report proves the feasibility and durability of fat graft transplantation for the treatment of HIV-associated lipoatrophy. In identical twins, genetic risks that could predispose toward lipodystrophy development were very unlikely to be in 1 twin but not the other. Because the patients were genetically identical, sympathetic nervous system denervation consequent to heterotopic transplantation may have protected the graft from lipolysis that would otherwise have been induced by humoral factors and autonomic neural regulation.

Pathogenetic mechanisms of lipodystrophy seem to be multifactorial and include host genetic factors, HIV, HIV-related immune alterations, and antiretroviral drugs (particularly thymidine analogue reverse transcriptase inhibitors). Imbalances in the autonomic nervous system, possibly mediated in part by antiretroviral therapy, may play a role in the development of lipoatrophy (4, 5).

Conclusion: Fat transplantation for HIV-related facial lipoatrophy seems to be a safe and effective treatment that can result in aesthetic improvements and greater patient satisfaction. This procedure warrants further evaluation among persons with HIV-associated lipoatrophy.

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References

Corrections

Correction: In the Clinic: Atrial Fibrillation
The recent In the Clinic on atrial fibrillation (1) contains several errors. On ITC5-5, under the heading “What underlying cardiac...?”, the sentence that currently reads “Some experts believe that the designation ‘lone atrial fibrillation’ should be restricted to patients older than 60 years of age...” should read “...restricted to patients younger than 60 years of age...” On ITC5-5, under the heading “What laboratory studies...?”, both instances of “ECG” in this section should say “echocardiogram.” In the Clinical Bottom Line Box for Diagnosis on ITC5-6, the end of the last sentence should read “...or contraindications to therapies, and echocardiogram to look for structural heart disease.” On ITC5-12, third paragraph, the third risk factor should be “...left-ventricular dysfunction on echocardiogram...” The online version of this In the Clinic has been corrected.

Reference

Correction: Addition of Sildenafil to Long-Term Intravenous Epoprostenol Therapy in Patients with Pulmonary Arterial Hypertension
In the recent article by Simonneau and colleagues (1), there are errors in Figure 2, panels A and B. In panel A, the 2 lines should be switched so that the top line is “Epoprostenol / sildenafil” and the bottom line is “Epoprostenol / placebo.” In panel B, the solid line should be labeled “Sildenafil minus placebo,” not “Sildenafil and placebo.” The online version of the figure has been corrected.

Reference