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Danby, F William

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COMMENTS AND RESPONSES

Health Care Costs

TO THE EDITOR: “Doc, if you can’t do a little better on that price, we’ll just have to let Mama go.” Doesn’t sound familiar, does it? It would if medicine were the 1-dimensional, market-driven enterprise that Dr. Bodenheimer presents (1). Clearly, there is a second dimension influencing health care decisions and utilization that is neither “market-driven” nor “rational.”

Anyone sorting through the estate of a loved one has encountered a 2-dimensional value system. Certainly, every item has a market value—that’s why we have eBay. But many items also have a sentimental value that cannot be expressed in dollars. This second dimension of value is independent of, additive to, and often greater than the item’s market value. This and other human values, such as the need to feel that the world is fair, safe, connected, and in control, define a dimension of nonmarket value that I broadly term *spiritual*. Unlike the market value of traded commodities, spiritual value cannot be bought, transferred, or even quantified, yet it still heavily influences decisions. As physicians, we are at times counselor, comforter, and conduit of hope. These are spiritual dimensions of our work.

Medicine is a *profession* precisely because we operate, in part, within the dimension of spiritual values. Except in extreme cases, our function and responsibilities within the spiritual dimension are unregulated and prevail beyond the influence of market forces. Instead, our actions within this domain are bounded by a public oath (usually Hippocratic), which defines unique and sacred responsibilities to our patients and peers. Publicly professing our common responsibility is what defines us as professionals, and acting in accordance with this professed obligation is professionalism. That physicians have professed the Oath for 3000 years reflects the centrality of this nonmarket value system to our work. To be a physician is a unique honor that derives from medicine’s spiritual dimension.

United States society routinely confuses *profession* with something one does for money (for example, professional golf), so we naturally have trouble understanding the role of spiritual values in medicine, including how such factors can drive health care costs beyond all bounds of economic reason. Although spirituality is personal and nonquantifiable, it is not economically or politically insignificant. In fact, opponents exploited this second dimension to doom the Clinton health care plan. If we do not acknowledge and seek to better understand this spiritual dimension of medicine, we will never fully comprehend medicine, much less the “drivers of health care costs.”

William L. Berger, MD
Medical College of Wisconsin
Milwaukee, WI 53226

Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Bodenheimer T. High and rising health care costs. Part 1: seeking an explanation. *Ann Intern Med.* 2005;142:847-54. [PMID: 15897535]

TO THE EDITOR: In his article describing how health care providers contribute to high and rising health care costs in the United States, Bodenheimer (1) notes that the quantity of services is associated with the supply of resources. Strategies to control supply, such as placing hospitals at risk for increased spending, could be effective in controlling costs. Such an approach was used successfully in Rochester, New York, in the 1980s (2, 3). From 1980 to 1989, the 9 hospitals in the Rochester area operated under an all-payer prospective payments system. This system, which featured local administration and control, represented the first time a group of hospitals in the United States had committed to a comprehensive regional financing system. Over the 9 years of the experiment, the rate of increase in hospital expenditures in Rochester was well below the national average while the financial position of its hospitals improved—the only hospital region in New York State that showed an operating surplus. A community-wide assessment showed no evidence of a reduction in the quality of care or access to health care. The experiment was terminated when competition and managed care became the mantra for controlling health care costs.

This regional system for hospital payment achieved high-quality care at an affordable cost through a balanced combination of self-regulation, cooperation, and competition. These words—regional system, self-regulation, balance between cooperation and competition—should serve as key principles for future attempts to improve the health care delivery system in the United States.

Paul Griner, MD

University of Rochester School of Medicine & Dentistry (retired)
Washington, DC 20016

Potential Financial Conflicts of Interest: None disclosed.

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Generic Drug Savings

TO THE EDITOR: We agree with most of Haas and colleagues’ statements (1) regarding the benefits of substituting generic drugs for brand-name drugs; however, we would like to stress that the authors assume that both the quality and the composition of generic and brand-name drugs are equivalent. From our pharmacovigilance experience in France and in Mauritania, we do not think this assumption applies everywhere. The use of poor-quality generic drugs could have obvious consequences when the long-term treatment of a serious condition, such as epilepsy, is at stake (2). Excipients that can induce cutaneous allergic reactions, such as macrogol, starch, indigotine, carmine indigo, or povidone, are frequently found in generic drugs but not in brand-name ones. The change in excipient content that occurs when shifting from a brand-name drug to a generic drug may modify bioavailability, generally reducing it. With such substi-

tutions, we observed hyperglycemia with gliclazide and blood pressure increases with diltiazem and verapamil.

If an adverse reaction to a generic drug occurs, hospitalization may be required to treat the response, and resumption of the brand-name drug is often the only way to continue the treatment safely. All these situations might increase costs.

Two other costly situations should also be mentioned. First, some pharmacists may mistakenly substitute an immediate-release generic drug for a slow-release brand-name drug. We experienced such a case with the drug mebeverine, a substitution that induced a vascular collapse. Second, regimen adherence in elderly patients is easily impeded, particularly by any change in the prescription to which they are accustomed. Substitution might be poorly understood by the patient, which could lead to the overlap of generic and brand-name drugs and possible toxicity or interruption in treatment (3). These types of changes carry the potential for adverse effects with associated costs that have not been widely evaluated. Consequently, the benefit drawn from generic drug use, although substantial, might be less than is usually considered.

Marie-Laure Laroche, MD
Louis Merle, MD, PhD
Hôpital Universitaire Dupuytren
87042 Limoges, France

Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: Drs. Laroche and Merle raise several issues about the potential risks of switching to a generic formulation. We agree that a generic drug may have different inactive ingredients, such as coloring agents, than the branded product. Uncommonly, an inactive ingredient may cause an allergic reaction. This is true for brand-name drugs as well as generics. In reviewing the literature, we found only a handful of case reports about allergic reactions to inactive ingredients, most commonly coloring agents.

In the United States, generic formulations are examined and approved by the Food and Drug Administration as being bioequivalent to a brand-name drug in safety, strength, and quality (1, 2). We cannot speak to the generalizability of our findings to other countries, which likely have different use patterns of brand-name and generic products. We agree that errors in drug dispensing are common and costly (3), but we know of no literature that suggests that they are more commonly associated with generic products. We believe that health care professionals, including physicians and pharmacists, should monitor patients with chronic conditions and inform all patients about generic substitution to avoid overuse and interruptions in treatment. We do not believe that these issues would substantially change the potential savings in drug expenditures associated with widespread generic substitution in the United States.

Jennifer S. Haas, MD, MSPH
Kathryn A. Phillips, PhD
Andrew C. Seger, PharmD
Brigham and Women's Hospital
Boston, MA 02120

Potential Financial Conflicts of Interest: None disclosed.

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Management of Menopause-Related Symptoms

TO THE EDITOR: The National Institutes of Health conference statement (1) notes that therapy with conjugated equine estrogen at doses equivalent to 0.625 mg increases the risk for serious disease events (specifically stroke, deep venous thrombosis, and pulmonary embolism) and, when combined with progestin medroxyprogesterone acetate, for coronary events and breast cancer. In studies in which women were treated for 5 to 7 years, increased risk for coronary and thromboembolic events started to emerge in the first year of use. Risk for stroke started to increase after 2 years of use, and risk for breast cancer started to increase after 3 to 4 years of use. Although experts theorize that long-term adverse effects associated with low-dose estrogens are lower, the precise risks and benefits are not known.

Note that the breast cancer risk shows up only when estrogen is combined with medroxyprogesterone acetate. This progestin is not a natural compound. To my knowledge, there is no known association of increased risk for breast cancer with natural progesterone. The fact that risk for breast cancer started to increase after 3 to 4 years of use is understandable: Alteration of the acinar and ductal systems in breast tissue takes time, which may explain the link to more recent exposure to medroxyprogesterone acetate, a chemical shown to produce worrisome changes in the ductal epithelium of mouse breast (2). The authors do not suggest the possibility that high levels of the natural human estrogens (estradiol, estrinol, and estrone) in early life might be responsible for inducing breast cancer at this later age. Likewise, the increases in thromboembolic disorders (both venous and arterial) are linked to the 10 or more equine pregnancy-related estrogens present in the specific product used in the Women's Health Initiative trials, not to natural human estrogens (3).

Last, to perpetuate the impression that all estrogens are alike is misleading. The trials referred to did not study the effect of estrogens—they studied conjugated, equine, pregnancy-related estrogens that have no place in the normal hormonal physiology of nonpregnant or nonmenstruating women. To tar all estrogens with the same brush is scientifically inaccurate at best and could, in my opinion, be seen as misleading or dissimulating for marketing reasons.

F. William Danby, MD
Dartmouth Medical School
Hanover, NH 03755

Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: Dr. Danby correctly notes, as reported in our statement, that the Women's Health Initiative randomized, controlled trial revealed an increased risk for breast cancer in women taking estrogen combined with medroxyprogesterone acetate (1). Although the safety profile for this progestin may differ from that of "natural" progesterone, this issue, to our knowledge, has not been studied in adequately powered randomized clinical trials. Of note, small studies that failed to meet established quality grading were excluded from the panel's purview. We feel that Dr. Danby is confusing the lack of well-designed studies to determine the safety and efficacy of other hormonal preparations with evidence of the safety of these preparations. Although large clinical trials of every formulation of estrogen and progesterone are not feasible, we caution the acceptance of this interpretation. We believe that, in the face of the adverse effects demonstrated by the Women's Health Initiative and other studies, the burden of proof may be best placed on demonstrating (rather than presuming) the safety of other formulations.

Dr. Danby cites the paper by Bhavnani (2), which lists the components of conjugated equine estrogens but does not provide any information for or against the safety of this preparation. Because our panel focused on the management of menopause-related symptoms, the correlation between high levels of endogenous estrogen early in life and breast cancer risk was not in our purview.

The panel did not intend to leave the reader with the impression that all hormonal preparations carry the same risk profile; instead, we based our summary on the preparations that have been studied in well-designed large clinical trials. Individual women and their health care providers will have to decide for themselves how far the safety and efficacy data from the Women's Health Initiative and the Heart and Estrogen/progestin Replacement Study (3) can be extrapolated to other formulations for the management of menopausal symptoms.

Carol M. Mangione, MD, MSPH
David Geffen School of Medicine at University of California at Los Angeles
Los Angeles, CA 90024

Donna L. Washington, MD, MPH
VA Greater Los Angeles Healthcare System
Los Angeles, CA 90012

Paul Woolf, MD, MBA
Crozer Chester Medical Center
Upland, PA 19013

Potential Financial Conflicts of Interest: None disclosed.

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International Committee of Medical Journal Editors' Definition of a Clinical Trial

TO THE EDITOR: Although I fully support the statements included in the editorial recently published in the *New England Journal of Medicine* about the registration of all clinical trials (1), I would like to pinpoint an important nuance concerning the stated definition of a trial: "Any research project that assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome." Neither this definition nor the International Committee of Medical Journal Editors' (ICMJE) 2004 editorial (2) include any mention of the type of assignment of human participants to the intervention and comparison groups. According to the principles of experimental design (3) and guidelines set forth by the CONSORT (Consolidated Standards for Reporting of Trials) statement (4), participants should be assigned to the comparison groups in the trial, ideally, through a random process. Nonrandom methods of assignment may be used, but such strategies carry several known limitations that can jeopardize the validity of a clinical trial and can be avoided with random allocation (3, 4). The CONSORT statement has been a very important contribution to the improved reporting of trials. The ICMJE and some leading medical journals, such as *Annals of Internal Medicine*, *Journal of the American Medical Association*, and *British Medical Journal*, have also been playing essential roles in this endeavor. Their efforts have improved the conduct, quality, and ethics of trials, highlighting such key methodologic aspects as masking, flow diagrams, intention-to-treat analyses, and reporting of harms. Consequently, for the sake of consistency and soundness, I believe that the ICMJE's definition of a clinical trial should read "Any research project that randomly assigns . . .," and these journals should insist on its importance and advantages.

Carlos Campillo-Artero, MD
Instituto Balear de la Salud
07003 Palma de Mallorca, Spain

Potential Financial Conflicts of Interest: None disclosed.

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IN RESPONSE: The editors of *Annals of Internal Medicine* wholeheartedly agree with Dr. Campillo-Artero's statements about the supremacy of randomized, controlled trials over trials that do not use random assignment. However, because the goal of the ICMJE policy on trials registration was to promote accessibility to clinically directive experimental research, the committee adopted a broad definition of clinical trials (1). Of note, the Ottawa Group, working closely with the World Health Organization to promote comprehensive trials registration, defines trials in an even broader manner than does the ICMJE. According to the Ottawa Group (2), *trial* refers to "a prospective controlled or uncontrolled research study evaluating the effects of 1 or more health-related interventions assigned to human participants." Recent trial registration efforts fully realize that randomized, controlled trials provide the most definitive evidence for causal relationships between interventions and health outcomes. However, other types of trials are sometimes the best available evidence to guide clinical practice. For this reason, the ICMJE believes that a comprehensive trial registry should contain information about any research project that prospectively assigns human participants to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome.

Christine Laine, MD, MPH
Senior Deputy Editor

Potential Financial Conflicts of Interest: None disclosed.

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CLINICAL OBSERVATIONS

Entoptic Phenomenon as Initial Presentation of Acute Myelogenous Leukemia

TO THE EDITOR: *Background:* About half of adult patients with acute myelogenous leukemia experience ocular involvement (1), most commonly leukemic retinopathy. In most of these cases, the retinopathy is asymptomatic (1–4).

Objective: To describe a patient with acute myelogenous leukemia whose initial presentation was a unique entoptic phenomenon.

Case Report: A 22-year-old man was referred to the ophthalmology clinic for evaluation of a superior dark semicircular shape in the central vision of his left eye that he had first noted 3 days earlier. The shape was fixed in position with movement of the eye. When the patient leaned forward, the dark semicircle increased in size, forming a full oval-shaped scotoma, and his vision became dark and clouded. As the patient returned to an upright position, his vision slowly improved and the scotoma regained its semicircular configuration. The patient also reported a 3-week history of malaise, fever, nausea, and vomiting. He had never used illicit drugs and took no regular medications.

On physical examination, the patient's temperature was 38.6 °C and his pulse rate was 130 beats/min. Bilateral cervical, axillary, and inguinal lymphadenopathy was present. The liver and spleen were moderately enlarged. On ophthalmic examination, visual acuity was 20/20 in the right eye and 20/30 in the left. He had marked bilateral conjunctival pallor. Results of funduscopic evaluation revealed bilateral intraretinal hemorrhages and white-centered hemorrhages affecting the left eye more severely than the right. A boat-shaped subhyaloid hemorrhage covered the inferior left macula, representative of

Figure. Funduscopy examination of the left eye.

Intraretinal hemorrhages, white-centered hemorrhages, and a boat-shaped subhyaloid hemorrhage covering the inferior left macula (top) are visible with the patient sitting upright. As the patient leans forward (bottom), the subhyaloid hemorrhage becomes circular in shape (arrows).

the shapes that the patient had described while sitting upright (**Figure, top**) and as he leaned forward (**Figure, bottom**).

Results of laboratory studies revealed marked pancytopenia with severe anemia (blood hemoglobin level of 48 g/L), platelet count of 27×10^9 cells/L, leukocyte count of 1.65×10^9 cells/L (10% peripheral lymphoblasts), and neutrophil count of 0.1×10^9 cells/L. Bone marrow biopsy confirmed the diagnosis of acute myelogenous leukemia.

Discussion: Acute leukemia can involve the eye by direct invasion of the orbit or ocular tissues, secondary vascular disruption (retinopathy), or complications secondary to central nervous system involvement (1–4). Leukemic retinopathy is characterized by the presence of tortuous, dilated retinal veins; nerve fiber ischemia or infarction; and varying combinations of intraretinal, subhyaloid, white-centered, and macular hemorrhages (1, 2). The white-centered hemorrhages are believed to represent aggregates of leukemic cells or a fibrin platelet plug surrounded by blood following capillary rupture. Retinopathy is more common in acute leukemia than in chronic leukemia and is thought to result from secondary hematologic abnormalities (1–4). Although the presence of retinal lesions has been associated with high leukocyte count, low platelet count, and low hemoglobin levels, the exact mechanisms involved and their significance remain unclear (1, 3).

Although retinal lesions are frequently asymptomatic (1–4), a few reports document patients with acute myelogenous leukemia who have ophthalmic symptoms (5). In the current case, the patient presented with an unusual entoptic phenomenon (a visual image arising from the intrinsic structure of the eye). He was able to visualize the shape of the subhyaloid hemorrhage present at the left

macula and, in effect, make his own in vivo hematocrit determination by changing his posture.

This patient's symptoms were unique; patients with acute myelogenous leukemia more commonly have blurred vision or loss of vision. Prompt recognition of the ocular manifestations aids in early referral for immediate treatment of this life-threatening condition.

Caroline Laforest, MBBS

Dinesh Selva, MBBS

John Crompton, MBBS

Igal Leibovitch, MD

Royal Adelaide Hospital

Adelaide SA 5000, Australia

Potential Financial Conflicts of Interest: None disclosed.

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CORRECTION

Correction: Work Disability Related to Musculoskeletal Disorders

A company affiliation was reported incorrectly for 2 authors of a recent article regarding musculoskeletal disorders (1). Drs. Lázaro

and Aguilar are affiliated with TAISS (Técnicas Avanzadas de Investigación en Servicios de Salud).

Reference

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