

Virtual Mentor

American Medical Association Journal of Ethics

June 2006, Volume 8, Number 6: 357-436.

Sound Prescribing

From The Editor

Rx for physician prescribing practices 359
Jennifer Reenan

Educating for Professionalism

Clinical Cases

Unnecessary antibiotics 362
Commentary by Jonathan A. Finkelstein

Hidden costs of free samples 367
Commentary by Richard Adair

The gift-giving influence 372
Commentary by Frederick S. Sierles

Prescribing placebos 377
Commentary by Perry G. Fine

Medical Education

E-prescribing 381
by Jorge G. Ruiz and Brian Hagenlocker

Journal Discussion

Patent (and public health) pending 387
by Philip A. Perry

Clinical Pearl

Clinical manifestations of vitamin B-12 deficiency 392
by Jennifer Reenan

Health Law

Neurontin and off-label marketing 397
by Christian J. Krautkramer

Policy Forum

- Reputation, gatekeeping and the politics of post-marketing drug regulation** 403
by Daniel Carpenter

Medicine & Society

- Direct-to-consumer drug ads, patient autonomy and the responsible exercise of power** 407
by Richard L. Kravitz and Jodi Halpern

Op-Ed

- “This may sting a bit”: cutting CME’s ties to pharma** 412
by Adriane Fugh-Berman and Sharon Batt
- Independence in continuing medical education** 416
by Murray Kopelow

Resources

- Suggested readings and resources** 420

June Contributors

- About the contributors** 435

Upcoming Issues of *Virtual Mentor*

July: State of the Art of Healing
August: Ethical Issues in Dermatology
September: Humanist Approaches to Care at the End of Life
October: Thresholds of Parental Competence in the Care of Chronically Ill Children

Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 359-361.

From the Editor

Rx for physician prescribing practices

One of the unique privileges and responsibilities accorded to medical practitioners, the act of prescribing drugs lies at the heart of the physician-patient relationship. Pulling the prescription pad out of the pockets of our white coats, pen in hand, signals to patients that we have help to offer, that we can give them something to alleviate or even eliminate the source of their complaints, and that their trust in the medical profession's collective knowledge, judgment and desire to serve is merited. Prescribing carries with it the promise of comfort and hope. Even since ancient times, it has been seen as an act of goodness. The well-known symbol Rx may even be derived from Egyptian hieroglyphics. According to the legend, Horus, the god of sky and of light and the keeper of secret wisdom, sustained a terrible eye injury while seeking to avenge the murder of his father. Later, the eye was magically healed. The eye of Horus thus became a symbol of health, now recognized as Rx, and its placement by physicians on written prescriptions represents an appeal for the success of the recommended remedy.

Recently, a multitude of front-page, ethically charged issues relating to prescription medications have been publicized and discussed in both the lay and professional press, sometimes calling into question the good intent behind prescribing and the ability of physicians to make sound prescribing decisions. Increased knowledge of the marketing tactics employed by pharmaceutical companies, in particular those directed at physicians, has prompted much-needed reflection within the profession about the influence such tactics may have on prescribing habits. Other headlines have raised concerns about drug safety, including the FDA approval and monitoring process for new drugs. Adverse events due to inappropriate or erroneous prescribing have also made the news, prompting numerous calls for computerized prescribing programs to assist physicians.

In this installment of *Virtual Mentor* we consider some of the challenges relating to the ethics of sound prescribing. Given the vast range of the topic, we have tried to highlight a spectrum of issues, from public policy trends in the area of post-market drug safety to appropriate medication choice in a pediatrics clinic. However, we have placed particular emphasis on some of the many dilemmas associated with the pharmaceutical industry. Growing public awareness of the potential conflicts of

interest between pharmaceutical companies and physicians will require us to navigate this relationship carefully in the future.

In the first case commentary, Jonathan Finkelstein, MD, suggests how a physician can respond to patient requests for treatments that are not likely to be of benefit. He also reflects on the dilemma faced by physicians who witness inappropriate prescribing by their colleagues. The second clinical case commentary, by Richard Adair, MD, delves into the hidden effects of free drug samples from pharmaceutical companies and offers some practical, clinic-based solutions designed to help patients acquire the drugs they need but may not be able to afford. Commenting on the third case, Frederick Sierles, MD, considers how medical students may be unconsciously influenced by free gifts, including the ever-popular gift of free food. In our final case, Perry Fine, MD, examines the prescribing of placebos and re-emphasizes the importance of the informed consent process and shared decision making in prescribing. In the clinical pearl, I take a brief look at vitamin B-12, once commonly, if inappropriately, prescribed as an injection for relief of fatigue and other non-specific symptoms.

A number of articles in this issue concern current trends in the law and government policy and how they may impact the ability of a physician to prescribe safe, appropriate and necessary medications. In this month's journal discussion, Philip Perry considers a recent proposal made in the *Journal of the American Medical Association* by Aaron Kesselheim, MD, JD, and Jerry Avorn, MD, to extend the legal principle of eminent domain to biomedical patents, permitting the government to use its authority during times of crisis to seize control of the production of biomedical products, thereby potentially increasing access to life-saving medications and vaccines. The policy forum section by Daniel Carpenter, PhD, reviews historical and current efforts by the federal government to reform the post-market regulation of drug safety. Dr. Carpenter points out that "reputational incentives" and a reluctance to reconsider standing FDA decisions may create a conflict of interest within the FDA between its Office of New Drugs, charged with pre-market approval, and the Office of Drug Safety, charged with post-market evaluation. Christian Krautkramer analyzes one of the more controversial prescription drug-related legal cases in the health law section, with a careful look at the off-label marketing tactics associated with the anti-seizure drug Neurontin.

Our medicine and society section explores patient autonomy in the face of an explosion of direct-to-consumer televised and print drug advertisements. In this section, Richard Kravitz, MD, MSPH, and Jodi Halpern, MD, PhD, also comment on the duties that patients have, as health care consumers, in the prescribing relationship. Jorge Ruiz, MD, and Brian Hagenlocker, MD, discuss the advantages and obstacles of e-prescribing/CPOE (computerized physician order entry) in the medical education section and consider the potential for e-prescribing to reduce medical errors. Finally, in the op-ed section, Adriane Fugh-Berman, MD, and her colleague Sharon Batt question the role of the pharmaceutical industry in continuing medical education, finding an inherent and possibly insurmountable conflict of

interest between educating and drug marketing. In a complementary op-ed article, Murray Kopelow, MD, chief executive of the Accreditation Council for Continuing Medical Education (ACCME), answers that the ACCME Standards for Commercial Support effectively maintain independent continuing medical education by separating education from drug promotion.

Of course, all physicians can remember the secret thrill of consulting the Tarascon Pocket Pharmacopoeia and carefully writing out our first prescriptions in medical school. Early in our careers, our greatest fear, perhaps second only to coming up with the wrong diagnosis, is of prescribing the wrong drug. In our concern to do no harm, I suspect that we younger physicians fail to reflect on what pressures, both internal and external, may be affecting our prescribing behavior. Prescribing drugs is something that experienced, practicing physicians do dozens of times daily, with great confidence but perhaps only rarely with consideration of the broader significance of the activity. Whatever your place on the medical education and training continuum, it is our hope that this month's issue will help you contemplate some of the social, political and, most importantly, ethical challenges related to sound prescribing, especially those pertaining to the influence of the pharmaceutical industry. In conclusion, I wish to express my gratitude to all of the authors for sharing their wisdom and expertise with our readers.

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 362-366.

Clinical Case

Unnecessary antibiotics

Commentary by Jonathan A. Finkelstein, MD, MPH

Dr. Waterman had a 12-year-old general pediatrics practice in a rapidly growing suburban community. Although well liked by his patients and their families, he found it increasingly difficult to thrive as a solo practitioner under a managed care system. After careful consideration, he decided to merge his practice with a fairly new pediatrics group in the same community.

During merger negotiations with his three new partners, Dr. Waterman agreed to a compensation formula based largely on the number of patients seen. His new partners, led by the ambitious Dr. Connolly, have also made no secret of their desire to increase the “market share” of the practice and the importance of securing a strong foothold in the community before more competition “moves in.”

In the winter, a few months after the merger, the office was flooded with anxious parents and their sneezy, sniffing and coughing youngsters. Ever since a medical school buddy told him about a case of community-acquired MRSA (methicillin-resistant *Staphylococcus aureus*) he had encountered, Dr. Waterman has been particularly sensitive to the threat of antibiotic resistance. He has therefore adjusted his prescribing pattern over the last few years to minimize antibiotic use. Although it requires more clinic time, Dr. Waterman is careful to explain to each parent why antibiotics might not be indicated for his or her child and what can be done to manage cough and cold symptoms at home.

The clinic was characteristically overbooked one Saturday in January, and Dr. Waterman was called in to see patients even though it was his day off. Assisted by Joan, the clinic nurse, he examined one of Dr. Connolly’s regular patients, a 4-year-old boy named Colby. Dr. Waterman told Colby’s mother that he suspected his symptoms were due to a respiratory virus and would not therefore prescribe antibiotics. She listened attentively to what he said and then became somewhat agitated, arguing that Dr. Connolly always gave Colby an antibiotic “just to be safe.” In fact, as she told him, she had spoken with Dr. Connolly that morning and he had specifically told her to bring Colby in for an antibiotic prescription. “Now, after listening to what you told me, I am just confused.” As the clinic nurse slipped out of the room, Dr. Waterman tried yet again to alleviate her anxiety and explain his reasoning.

Suddenly, Dr. Connolly opened the door and burst into the examining room with Joan at his side and gave Colby and his mother a big smile. “Everything going all right?” he asked. “I have your prescription right here. Sorry about the delay.” Later on, Dr. Connolly sympathetically told Dr. Waterman that making parents you haven’t met before “happy” isn’t always easy and that he was glad he could “help out” with Colby’s case.

That evening, after everyone had left the clinic, Dr. Waterman looked through every one of the past week’s charts. He noticed that Dr. Connolly and the other two pediatricians regularly prescribed antibiotics inappropriately. He also observed that they each managed to see about 20 percent more patients than he did.

Commentary

The case of Dr. Waterman and his young patient Colby is an example of two general and quite common dilemmas faced by all clinicians: first, how should a physician respond to patient requests for treatments that are unlikely to be of benefit, and, second, how can a clinician maintain his or her own professional integrity when practicing in a group with different clinical approaches or values. The former is an example of what might be considered a “low impact” ethical decision. Whether or not Colby receives a single course of an antibiotic is not likely to be a life-and-death event for him or anybody else. The potential benefits may be negligible, but the potential harms to Colby are small as well. However, we should concern ourselves with the ethical issues surrounding this case because the “low impact” decisions we make over and over again, in aggregate, do have consequences for our patients, for the populations we serve and for us as professionals. Dilemmas about the use of antibiotics are also complex because they call on us to weigh potential benefits and harms to an individual with those that may accrue to the population at large. In this country, in particular, the focus of medical professionals has been almost exclusively on the benefits and harms to individuals, with less regard for the consequences to public health more generally [1].

It may be helpful to divide patient requests for ineffective treatment into several categories. In some cases the treatment, though not helpful, will be quite unlikely to harm the individual or the community; in others, it carries a risk of harm to the individual but not the community; and in still others, the treatment, though safe for the individual, carries a risk for the community. Unnecessary antibiotic use primarily falls into the last category—the one that is perhaps the most ethically and interpersonally challenging for physicians. So what are the likelihood and magnitude of harms from unnecessary antibiotic use? For individuals, the risk of carrying antibiotic-nonsusceptible organisms increases (for a limited period) after a course of antibiotics [2]. Colby’s mother should know that there is a small risk of harm to Colby himself associated with taking an antibiotic. This small risk is outweighed when we use antibiotics appropriately for treatment of bacterial infections but not when prescribed for viral illnesses. Estimating the harm to the community is quite difficult. High rates of antibiotic use are widely believed to have contributed to increasing rates of antibiotic resistance among human pathogens [3, 4]. And resistant

infections are harder to treat [5]. In one study, Coast has articulated the difficulty of estimating the aggregate, long-term harm to the population because of diffuse nature of the effects, comparison of current and future benefits and harms, uncertainty about the future course of resistance, and the possible development of new antibacterial agents, among other reasons [6]. Thus, the harm of any individual course of antibiotic (appropriate or not) is unknown, but small.

The professional integrity issues raised in this case overemphasize the role of financial pressures on physician practice, suggesting that the primary driver of the differences in clinical care between Dr. Waterman and new colleagues is their approach to surviving in a financially competitive environment. That there are significant financial pressures on physicians in practice is not in doubt, and these may have increased over recent decades. It is also true, though, that even in the halcyon days of fee-for-service medicine, there were incentives for physicians to keep their patients “happy.” In fact, increases in antibiotic use in this country have occurred over decades [7]. It is also not merely a new function of managed care that professionals in practice groups disagree on both the financial aspects of their partnership or the correct approach to managing common clinical conditions.

So, to review the situation:

1. Colby has a terrible viral upper respiratory tract infection.
2. We have the potential harm to the community of unnecessary antibiotic use, which is quite small if we consider just one additional antibiotic prescription but potentially large (though unknown) when we consider unnecessary antibiotic prescribing in aggregate.
3. The beleaguered Dr. Waterman has his financial survival on the line along with his professional integrity as an evidence-based physician.

As is often true in clinical dilemmas, the best course lies in optimizing communication and interpersonal negotiation—with both patients and colleagues. Dr. Waterman failed in his attempt to help Colby’s mother understand that an antibiotic will not help her son. In this particular case, it may have been an impossible task. Patients learn from their clinicians *over time*, and it may be difficult for a covering physician to change a longstanding pattern of treatment. Some data suggest, however, that what is perceived by physicians as a demand for unnecessary antibiotics is really just a request by parents for more information on diagnosis and effective treatments [8]. Whether or not prescribing antibiotics judiciously takes more time in practice is debatable. But, since we are largely responsible for the expectations of our patients, we can train the next generation to understand better the natural history of viral illness and the risks of antibiotic resistance. Increased public awareness regarding antibiotic overuse is one likely reason for the recent dramatic decreases in antibiotic prescribing in this country [9, 10].

In the end, the resolution with Colby’s mother about this single course of antibiotic is less important than the resolution of the differences between Dr. Waterman and his

practice partners. If he could catalyze a shift of this practice toward more judicious antibiotic use, he would be reducing the exposure of his community to thousands of antibiotics. How could Dr. Waterman raise this issue? One approach is to focus the practice group on *consistency* of practice in this and other key areas. That is, if one partner always prescribes antibiotics for 7 days of green runny nose and another does not, we can hardly blame patients for being confused about the appropriate treatment. Dr. Waterman might engage his colleagues in a conversation that begins with, “Wouldn’t it be helpful if we agreed on treatment strategies for the very common problems that we frequently see in each others’ patients?” It may be easier to bring available evidence to the table in this discussion than to argue about management of an individual case.

Certainly, such conversations happen more frequently in some practices than in others. Whether or not Dr. Waterman can remain with this practice group depends on whether he is able to engage them in such conversations. Variation in clinical skill, motivations for practice and even professional ethics will always exist. And clinicians may not have complete control over all of the partners with whom they work. Dr. Waterman will need to decide, over time, whether he is comfortable with the quality of care he can provide with this group of colleagues. For Colby, the issue is not really a single antibiotic prescription but antibiotic prescribing in aggregate and the levels of resistance in his community. Similarly, the issue for Dr. Waterman is not really a single 4-year-old with a runny nose, but an approach to evidence-based medical care, consistency in practice and integration of both individual and population ethics in decision making.

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 367-371.

Clinical Case

Hidden costs of free samples

Commentary by Richard Adair, MD

Dr. Martinez has joined a new rural primary care practice that is affiliated with the academic health center where she just completed her training in general internal medicine. Although nervous about the responsibilities she now has as a practicing physician, she is excited to be working on a daily basis with the medical director of the health clinic, one of her favorite and most trusted mentors, Dr. Francis. The clinic is staffed by two other internists, a physician assistant and three nurses.

Dr. Francis asked Dr. Martinez to be responsible for organizing educational events for the staff including arranging conferences with pharmaceutical sales representatives. A firm believer in the principles of evidence-based medicine, Dr. Martinez relies upon the best-available medical literature for her therapeutic recommendations and is highly skeptical of the educational benefits of pharmaceutical sales presentations. In her experience, the information provided by representatives is usually misleading or, worse, inaccurate. In fact, she was pleased to learn that the academic health center where she did her residency recently decided to bar drug representatives and equipment vendors from visiting its staff without appointments.

During her first few weeks at the clinic, Dr. Martinez was shocked to have received more than two dozen phone calls and e-mails from pharmaceutical sales representatives. After congratulating her on joining the new clinic, they went on to offer her free educational seminars for the staff as well as lots of potentially useful free samples—including a new antihypertensive, birth control pills and allergy medications.

Dr. Martinez schedules a meeting with Dr. Francis to discuss these various offers. He understands her concerns about the validity and substance of the educational material distributed by the drug reps but reminds her that many financially strapped rural patients must pay out of pocket for their medications. Establishing good rapport with some of these pharmaceutical companies and getting a regular supply of free drug samples could be of enormous benefit to our patients, argues Dr. Francis.

Commentary

Dr. Martinez is right to be skeptical about the value of using pharmaceutical

representatives for continuing medical education. Her viewpoint is supported by national organizations like the American College of Physicians [1]. Let's face it: all initiatives from pharmaceutical companies include the goal of marketing their products [2]. They're hard to escape; a "white coat check" at one teaching hospital found items bearing pharmaceutical company brand names in the pockets of 97 percent of residents [3].

How will Dr. Martinez handle what sounds like a difference of opinion with her mentor and new partner? I hope she realizes that her commitment to evidence-based practice and unbiased sources of information are part of why she was recruited and hired. Teachers learn from their students, and older physicians look to new partners for help in keeping up to date. I would encourage her to give her views freely and directly. If Dr. Francis is unconvinced, she can still do what is right for her. The office receptionist could say, "some doctors in our practice see reps and others don't." She can also respect her partners' views; we don't all have to do everything the same way.

Samples: just how helpful?

The controversy in this case relates to the "free" sample medications Dr. Martinez is offered. In surveys, both residents and practicing physicians think samples are ethically more acceptable than gifts like meals, pens and reflex hammers because they "help" patients [4]. But do they?

In the short term, samples are helpful for patients who would otherwise go without medication. But sample drugs are more expensive than over-the-counter or generic alternatives, and physicians have a strong tendency to continue to prescribe what a patient is already taking rather than switch to a drug they would normally prefer [5]. Patients quickly develop brand loyalty. So what is helpful and free in the short run will probably increase costs later.

What about the effect on Dr. Martinez? Most physicians believe they can do what's right for their patients and resist the same marketing that influences their peers [6]. In other words, we think we're all above average (as in the fictional Lake Wobegon) and somehow immune from advertising pressure. At our clinic, we looked at this in a randomized trial [7]. We divided our residents into two groups, one with and one without sample access, and made a list of heavily advertised drugs that showed whether a less expensive generic or over-the-counter alternative was available. We found that the residents with sample access were less likely to prescribe unadvertised drugs or over-the-counter drugs. They developed expensive prescribing habits that may be hard to change later.

Also, some ethicists worry that giving patients a gift with significant monetary value puts a different spin on the patient-physician relationship, creating an imbalance of power rather than working toward a partnership based on mutual responsibility.

Other ways to assist patients

Dr. Martinez's choices include using samples regularly, never using samples, or using them rarely and only as a last resort. Her decision will be easier if she can identify other ways to help her patients manage drug costs.

She could learn the costs of drugs she commonly uses (easily available online) and make a habit of choosing the least expensive alternatives. Because patients often keep their financial worries to themselves, she could decide to do this for all her patients.

She could form the habit of regularly discontinuing medications that aren't necessary. Some patients seem to accumulate medications like barnacles.

When asking what medications her patients are taking, she could include the question, "Do you have any trouble getting them?" A nod, or even a raised eyebrow, could signal the need for further questions and perhaps a referral for help. She could be aware that certain demographic groups, such as the elderly, low-income patients and members of minority groups are especially likely to "stretch" medications to save money [8].

She could propose a more systematic approach for her group practice. Realizing that circumstances vary, I will describe some things we've tried in our inner-city clinic, where many patients don't speak English and almost half report not taking prescribed medications because of cost.

One of our receptionists now dedicates one morning a week to helping selected patients fill out paperwork for the "free drugs by mail" programs that most major pharmaceutical companies offer indigent patients. This provides an opportunity for our triage nurses to refer patients for assistance and builds good will.

We hired a part-time social worker to find out whether patients qualify for Medicaid and guide them through enrollment. This employee also signs up patients for Medicare Part D and answers questions about importing drugs from outside the U.S. To come up with her salary, we organized a fundraiser and successfully competed for some philanthropic funds. We were surprised how many people in our community were willing to contribute. Even the mayor showed up.

We asked a local pharmacy to provide a list of the cost of some commonly used medications for hypertension and posted this information by the X-ray view box where doctors would see it every day. We also posted guidelines for hypertension treatment. After 16 months, we were using more thiazides and fewer calcium channel blockers. The average cost per drug decreased for our patients while hypertension control rates improved [9].

We stay in touch with friends working in similar clinics and listen for new ideas.

Some of our doctors have had conversations with local leaders, including members of the state legislature, about the problems our patients face. We don't have all of the answers, but we can perhaps help them understand the extent of the problem.

We strongly considered refusing all samples, a recommendation with which we sympathize [2]. Instead, we decided to keep our sample cabinet but limit what's in it to a few essential drugs. We use it mostly with patients who are waiting for the "free drugs by mail" to arrive, usually about a month. We don't give samples to patients whose insurance covers medications. We don't give samples when a less expensive drug in the same class is available generically or over the counter. We do have obligatory conversations with the drug representatives, but keep them brief and in the hallway.

This compromise isn't perfect but it's workable, for now.

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Related articles

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[Educating patients about the cost of medications](#), March 2006

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 372-376.

Clinical Case

The gift-giving influence

Commentary by Frederick S. Sierles, MD

It's late Friday afternoon in the residents' lounge of the Department of Surgery at Metro Academic Medical Center. A few on-call interns are napping on the tattered couches. Others who have just finished their shifts are making plans for later that evening. Someone from the chair's office is stuffing mailboxes with an invitation to a summer picnic. Along one wall, a pharmaceutical sales representative sets up a long table with the city's best pizza and a large supply of bright purple penlights, pins, logo-emblazoned pens, notebooks and stuffed toys. Three third-year medical students—Michael, Carly and Holly—are the first to grab a few hot slices and a pen or two and to greet the smiling sales rep, who tells them about a new addition to the hospital's formulary.

Friday afternoon pizza is part of what they jokingly call their regular "food rounds." Only two months into their third year, they have quickly learned when and where free food might be found in the hospital. Tuesdays there is free lunch during the department of internal medicine grand rounds. Wednesdays there are bagels and juice during the department of pediatrics morning report for residents and students. And cookies, brownies and coffee regularly appear on the psychiatry and neurology floors. They never mind talking to the sales reps at these things, although they tend to stuff the glossy literature into their bags and forget about it.

Michael has even become friendly with one of the sales reps who encouraged him to apply for a grant sponsored by the pharmaceutical company. With the money he was awarded, Michael was able to attend a pediatrics conference in Miami.

A few weeks later, the three friends attend a required meeting of all third- and fourth-year medical students where they are lectured about various pharmaceutical sales techniques, including how gift relationships can create a sense of obligation. Michael, Carly and Holly meet up in the hall afterwards to discuss the presentation. They all scoff at the idea that their future prescribing habits will be influenced by a slice of pizza and a pen. "How naïve do they think we are?" asks Carly. "We're scientists, not gullible spectators," protests Michael. The dean of students, Dr. Markovsky, overhears their conversation and wonders if it is time to start seriously considering banning all pharmaceutical industry-promoted activities to prevent prescribing bias.

Commentary

Everyone who has practiced medicine will easily empathize with the students. By late Friday afternoon, most everyone is tired, and, if patients are attended to and a good transition is made to the evening shift, thoughts of an evening's relaxation, camaraderie or romance emerge among those who are not on call. What else comes to mind and how the students act depends on what happens next.

If a patient is newly admitted and time remains on the shift, Michael, Carly or Holly will eagerly join a resident to begin care of the patient. The more responsibility the student, say Carly, takes under skillful supervision, the more she will benefit. *The three students know the event's implications*—good diagnosis and treatment will usually restore the patient's health, Carly's education will be enriched, and, if the case is discussed on subsequent rounds, Michael's and Holly's educational experiences will also be enhanced. This is the heart and soul of clinical education.

If there are no new admissions, and *if the three are typical students at a typical school* [1], *they will not think about the implications of accepting the food and gifts*. Most likely this undoubtedly bright, altruistic threesome will eat the pizza, take a gift advertising the drug and schmooze with the young, attractive empathic rep who will present information favoring the drug, which was requested for the formulary by a physician more likely than others to have accepted company gifts [1]. They won't know which rep statements are biased, will enjoy the food and friendliness and will deny being influenced. Essentially, they will act like most of their physician role models.

Dean Markovsky, duly concerned about similar interactions and contemplating banning visits from reps, has thoughtfully required that the students be taught about industry-physician relationships [2]. However, because students' formal education has probably been counteracted by their experiences with role models within a hidden curriculum (e.g., seeing supervisors accept gifts), this education will have been too brief and not sufficiently persuasive to change their attitudes meaningfully [1, 2]. Dean Markovsky, the other deans, the faculty, the students and the medical center have established no restrictions about drug rep-student relationships (only 9 percent of schools have restrictions). Anyone proposing decisive restrictions may have to lock horns with influential faculty members who have industry ties [2].

For these three typical students becoming typical physicians, the implications of this scene and tens of thousands of similar scenes are that prescribing will continue to be inconsistent with evidence-based guidelines. Formulary requests will be made for new drugs that have no clear advantage over existing ones, and nonrational prescribing and the prescribing of costlier drugs and fewer generic drugs will continue. This interaction with a sales rep is one of 60 million annual U.S. "details" in national marketing campaigns that contribute to shockingly expensive drug costs [1]. The students' gravitation to "free food" misses the point that the food and Michael's conference in Miami are anything but free, and the company is buying their good will, setting the stage for receptivity to future offers.

Why do they feel impervious to marketing's influence, even after being taught about physician susceptibility? Students are strongly influenced by physician role models, and most physicians feel immune to marketing's influence, despite clear evidence to the contrary [1]. Some suggest that physicians' denial of influence reflects self-serving bias—a universal human tendency to overrate oneself and believe one will engage in desirable behaviors with favorable outcomes [3]. “On average [4], people say they are ‘above average’ in skill (a conclusion that denies statistical possibility),” a Lake Wobegon—“where all the children are above average”—effect.

Self-serving bias is near-universal [4]. Business leaders believe their company is more likely to succeed than the average firm; people feel less susceptible than others to the flu. So, also, Steinman et al found that 61 percent of residents believed colleagues' prescribing practices were influenced by marketing, but only 16 percent felt susceptible themselves [5].

How do “small” gifts affect prescribing? Katz et al [3] cite the persuasive influence of small gifts, sometimes exceeding that for large gifts. “When a gift or gesture of any size is bestowed, it imposes... a sense of indebtedness.... The... rule of reciprocity imposes... an obligation to repay for favors, gifts and invitations.... Feelings of obligation are not related to the size of the initial gift or favor.” For example, the success secret of the world record holder for car sales was sending mass-produced greeting cards to his customers containing the phrase, “I like you.” Similarly, when the Disabled American Veterans appeals by mail, the response rate is 18 percent when no gift is included, but 35 percent when envelopes contain an unsolicited gift [3]. Food, flattery and friendship are all powerful tools, and individuals tend to be more receptive to information they receive while eating enjoyable food [3].

Moreover, the symbolic meanings of small items can be huge. Wearing a necklace with a religious symbol or having a Confederate flag bumper sticker sends a strong message about oneself. If a doctor carries a pen advertising a drug, some will perceive him or her as a walking drug company billboard.

We don't know for sure what educational, political or regulatory interventions are most needed to profoundly strengthen the industry-professional boundary, but there are some signs of progress. Civil rights activist Hollis Watkins said there are four stages of successful advocacy: investigation, education, negotiation, and—if this is insufficient—demonstration [6]. During the past decade, reports from extensive investigations of drug company-doctor interactions by scientific, journalistic and consumer-advocacy organizations have been widely disseminated. There is enough data for a substantial course that would include characteristics of the pharmaceutical industry; bringing drugs to market; contributions of industry, government and academia to pharmaceutical research; industry influence on scientific literature; types of drug company-physician interactions and their influence; physician denial; characteristics of information presented by companies; industry scandals; efforts to reduce influence on trainees' behaviors; and tips on how to interact or eschew

interaction with drug company representatives. Because evaluation influences curriculum, the National Board of Medical Examiners (NBME) should test these topics.

Most U.S. schools teach about the topic, but in 30 percent of schools the teaching is limited to a single class session. Faculty members are less likely to perceive that their objectives have been met than colleagues whose schools teach more extensively [2]. Trainees in residencies that restrict exposure to reps and students in medical schools whose hospital restricts contact are less likely than others to meet reps or deny influence [1]. Simply having a policy, however, is insufficient to influence trainee behaviors if the policy is unknown or unclear to students or if physician role models accept gifts [1]. Of course, some students and physicians will have the wisdom and courage to refuse gifts regardless of role model behaviors, restrictions or classes.

Progressively more doctors and organizations now advocate complete bans on physician receipt of gifts. Partial restrictions are usually ambiguous, hard to remember or adhere to, contradict other restrictions, are usually unenforceable, and underestimate the strong influence of small gifts. Because many influential persons and powerful organizations and companies will oppose complete bans tooth and nail, public demonstration may become necessary.

I thank Nessa Meshkaty and Terrie Stengel for their helpful suggestions.

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 377-380.

Clinical Case

Prescribing placebos

Commentary by Perry G. Fine, MD

Dr. Gibson, a second-year family medicine resident, spends two afternoons a week working in a busy urban clinic. His attending physician, Dr. Marshall, asks him to see a patient named Ms. Wood. “She’s a challenging patient, but not in the medical sense,” she winks at him. “Just try not to spend too much time in there,” she further cautions. “A regular frequent flyer,” says one of the medical assistants handing Dr. Gibson the chart. He glances through the 3-inch thick file quickly as he walks down the hall to the examining room.

Ms. Wood has had a surprising number of medical workups for a person of 39 who is, on the whole, pretty healthy, though overweight. Two weeks before she had undergone a complete cardiac workup, including a stress test. With the exception of a finding of chronic hypertension, all of her extensive diagnostic testing has been normal. Her current medication list includes an antihypertensive and a variety of vitamin supplements. Today she says she is terribly fatigued and has some “pretty bad stomach gas” pain at night. “I just can’t seem to get out of bed these days, Doctor,” she tells him. “You’ve got to give me something to boost my energy!” Dr. Gibson performs a careful physical examination, including a complete abdominal exam, the results of which are unremarkable. He suspects, based on further discussion, that her gas pains are due to gastroesophageal reflux disease (GERD) and tells her that he will prescribe an antireflux medication. He also spends some time explaining measures she can take to minimize her reflux symptoms. “But what about my fatigue?” she complains. “You haven’t given me anything for that and it’s worse than the stomach thing!”

Dr. Gibson sympathetically agrees with her and tells her he needs to step out for a few minutes to discuss the fatigue with her regular physician, Dr. Marshall. He is firmly convinced that Ms. Wood would benefit from a psychiatric evaluation and treatment for anxiety or depression, but he has not seen any mention of either in her chart. Her blood work from two weeks ago rules out thyroid problems and anemia as possible causes for the fatigue.

“I am sure that you must have considered a psychiatric condition at some point?” queries Dr. Gibson. “Of course,” says Dr. Marshall, “but she absolutely refuses to meet with a psychiatrist and she will not take any psychiatric medications for

insurance reasons. She is afraid that she will lose her life insurance if she has a documented history of being treated for depression or anxiety.

“I’ve just been giving her some herbal and vitamin therapy and occasional shots of vitamin B-12, which seem to help her energy levels,” reveals Dr. Marshall, “and I’m encouraging her to exercise, of course. A B-12 shot should do the trick for a few more weeks at least,” he tells Dr. Gibson. “Go ahead and have the nurse draw it up.”

Commentary

The presumption in the case of Ms. Wood is that, because no specific etiology is identified for her complaint of fatigue, her physician decides that a nonspecific treatment (injection of vitamin B-12) is warranted to relieve her symptoms. In and of itself, this is not necessarily “bad medicine,” given adequate assessment and thoughtful balance of benefits versus burdens of both the further evaluation and the treatment chosen. The real fault in this case is the failure of Drs. Gibson and Marshall to engage the patient in an open, honest discussion of risks, benefits and alternatives; in other words, to seek her informed consent. Translated into ethical terms, the patient’s autonomy has not been respected. This may not be of concern to Ms. Wood, but how can her physicians know, if she is not given the opportunity to engage in open, frank discussion? Not only has her regular physician used a subordinate in the commission of this act, a rather minor trespass in itself, but she also failed to model key elements of the patient-physician relationship: mutual trust and shared responsibility for health care decisions [1].

Whether or not vitamin B-12 is beneficial for nonspecific fatigue is debatable, and so it is a questionable example upon which to base a discussion about placebo use in clinical practice. A search of the Cochrane Collaboration Library on the evidence for efficacy of B-12 for this indication is not revealing, but countless anecdotal reports and at least one small crossover placebo-controlled clinical trial suggest some benefit with virtually no harm [2]. Sadly, this level of evidence is not too much different from the level upon which many other routine clinical practices are based. So why didn’t the physician opt for candor and say, “I think your fatigue would be greatly improved by exercise and other healthy lifestyle choices, but I am willing to give you a shot of vitamin B-12 because it has very little risk of causing harm, except for the cost, and maybe it will help you get motivated enough to start the supervised exercise program I am going to prescribe. What are your thoughts about that, Ms. Wood?”

But what if an inactive placebo such as isotonic saline were chosen by the physician instead of the disputable B-12 injection? In that case, the breach in the patient-physician relationship extends beyond insufficient engagement of the patient in the treatment plan and into the more troubling realm of frank deception. Physicians are ethically obligated to promote patients’ welfare by balancing the anticipated benefits of a given intervention against its potential harms. Deception undermines patient trust, erodes the patient-physician relationship and can potentially result in medical harm to the patient [3, 4]. Full disclosure of the (possible) use of an inert substance

that may result in a therapeutic effect (the placebo effect) or an untoward effect (the “nocebo” effect) legitimizes active or inactive placebo controls in clinical research, including “n of 1” clinical trials [5, 6]. This ethical “safe harbor” cannot be invoked when a patient is intentionally misled [7].

Dangers of deception

If patients learn that they have been fooled intentionally by their doctors (for perhaps well-intended but nonetheless spurious reasons), how will they be able to regain confidence in the medical profession? Although difficult to measure, this betrayal may carry more profound and enduring harm, negatively impacting the present and future relationships between the patient and health care professionals, including their willingness to seek help when it is needed. This is a high price to pay to learn how suggestible a patient is or, worse, simply to avoid a difficult conversation with a poorly compliant patient.

In summary, the relief of pain, fatigue and other distressing symptoms is a fundamental duty of medical doctors, and relief is what patients commonly seek from us, whether or not a cure is possible. Recent years have brought vast improvements in our palliative capabilities, especially in treating patients with well-defined etiologies for their signs and symptoms. But we still struggle to help patients with ill-defined medical—much less emotionally based—causes for constitutional symptoms such as fatigue. The use of placebos in clinical practices marginalizes patients with these sorts of complaints. Failure to use effective therapies or, in their absence, the power of the relationship itself in favor of placebos puts the patient at risk and makes the practitioner highly vulnerable, subject to ethical and, perhaps, legal sanctions. Concern over the use of placebo as a medical expedient has caused several medical professional organizations to create policies proscribing their use [8, 9]. The American Medical Association’s Council on Ethical and Judicial Affairs is in the midst of creating a report on this topic, admonishing against the deceptive use of placebos in (nonresearch) clinical practice, which should be issued within the year [10].

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Related article

[Clinical manifestations of vitamin B-12 deficiency](#), June 2006

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 381-386.

Medical Education

E-prescribing

by Jorge G. Ruiz, MD, and Brian Hagenlocker, MD

Both the federal government and private sector experts have recommended the use of electronic prescribing, or e-prescribing, as a response to the problem of adverse drug events. The Institute of Medicine report, “To Err Is Human: Building a Safer Health System,” exposed the serious nature of this category of medical errors [1]. Most such errors occur during the process of ordering medications [2]. E-prescribing refers to the computerized ordering of specific medications for individual patients by clinicians [3]. A key component of e-prescribing software is often a clinical decision-support system (CDSS), an information system designed to improve clinical decision making [4]. These CDSS systems may be rule-based systems that provide information about drug interactions, drug-diagnosis interactions and drug-allergy problems. They may also include treatment algorithms, information about alternative medication regimens, and computer-based clinical pathways, or may have more advanced scoring and expert systems that assist clinicians by providing reliable and objective estimation of disease prognoses, probability of adverse events and outcomes.

E-prescribing is generally the core function of a more comprehensive computerized physician order entry (CPOE) system that allows clinicians to order not only medications but also diagnostic tests, patient care activities and referrals [5]. Advocates claim that e-prescribing increases accuracy and legibility of prescriptions, integrates the prescription information into electronic medical records, helps physicians adhere to hospital formularies and is cost-effective [6]. The advantages of e-prescribing translate into reduced medical errors and potentially better patient outcomes [7]. Despite these purported benefits, hospitals and clinics have been slow to adopt e-prescribing systems, principally because of the substantial cost of acquisition and set-up [8], resistance from physicians or administrators, concerns about privacy and discrimination, and vendor immaturity [9].

Critics maintain that the introduction of e-prescribing into clinical practice requires substantial organizational changes and may unintentionally disrupt the clinicians’ workflow. They point out difficulties in calculating return on investment; concerns about physicians taking too long to input an order, resulting in poor compliance with recommendations; and a lack of research evaluating different models of system implementation [10, 11].

The evidence base

Indeed, potential benefits aside, there is no evidence that e-prescribing systems with or without clinical decision-support systems result in any significant decreases in morbidity and mortality [4, 12]. Most of the evidence refers to improvements in the process of care and practitioner performance. On one hand, it's true that initial studies demonstrated substantial reductions in medical errors and potential and adverse drug reactions in tertiary academic medical centers with homegrown e-prescribing systems and rudimentary decision support [7, 13]. These studies also yielded limited evidence of decreased lengths of stay and overall hospital costs [14]. On the other hand, early evidence in one of the "successful" studies also revealed an increase in potentially life-threatening adverse drug events due to a system bug in the process of ordering potassium infusions [15]. Growing evidence of both homegrown and vendor-developed products revealed disturbing findings, including frequent medication error risks [6], higher rates of adverse drug events despite the high use of a CPOE-based e-prescribing system at a Veterans Affairs hospital [16], elicitation of intense and mostly negative emotional responses from physicians after implementation of e-prescribing [17], and an association with increased mortality in a seriously ill pediatric population [18].

Have we then traded one set of problems for another? This evidence does not disqualify e-prescribing and computerized physician order entry as valuable tools for clinicians. The rational and effective use of e-prescribing requires that administrators, developers and clinicians pay careful attention to potential problems through a continuous quality-improvement process after implementation [19]. E-prescribing solutions often require the customization of systems for diverse health care institutions in academic, urban or rural locales. They must adapt to specific settings of care such as outpatient, inpatient, medical-surgical services, intensive care or emergency departments. The computer applications are also asked to account for the various patient populations—children, adult, elderly—served by those institutions [11, 19]. But the interactions between humans and computers are often unpredictable [19]. The ultimate goal should be the implementation of e-prescribing systems as part of a more comprehensive electronic medical record system, as proposed by the federal government and others [20].

The role of e-learning in better physician prescribing

If e-prescribing's main purported advantage is the improvement of physician prescribing and reduction of medical errors, it may be particularly useful for busy clinicians caring for a growing number of patients. Physicians do face tremendous challenges in trying to follow up on answers to a multitude of relevant drug-prescribing questions within serious time constraints [21]. This problem is further complicated by the expansion of the body of evidence-based medical knowledge and the increasing number of available medications and potential adverse drug reactions [21]. Continuing medical education (CME), the usual approach clinicians use to deal with these challenges, is nonetheless rather ineffective and inefficient for this purpose in its traditional form [22]. Internet-based CME shows signs of being more effective [23].

E-prescribing offers to improve physicians' prescribing practices at the point of care through the use of information technology and e-learning interventions. E-prescribing systems with computerized decision support systems may allow clinicians to receive just-in-time training that is cued by patient care activities and made feasible by the ubiquity of computers in the clinical environment and the expansion of mobile wireless technologies. The linkage of e-prescribing and computerized physician order entry systems with e-learning can promote this process through the use of Internet-based technologies to enhance education and training [24]. E-learning materials integrated into an e-prescribing CDSS may consist of a range of electronic resources [21], including:

- access to medical databases (e.g., PubMed, Cochrane Library, EMBASE)
- electronic books and journals
- e-learning tutorials and simulations
- scientific drug information (e.g., Micromedex, Physicians' Desk Reference, FDA)
- patient education resources (e.g., Medline Plus)

One of the key features of this integration is the simultaneous access to individual patient information including medication history and relevant drug information in e-learning databases, thereby ensuring safe and effective prescribing without forced disruptions to the clinicians' workflow [21, 25]. The seamless integration of these e-learning materials into clinical decision support systems and e-prescribing fosters evidence-based, rational and individualized prescribing. It is also conceivable that physicians at the point of care may receive CME credits for some of these activities, which would further encourage the use of evidence-based interventions. The AMA is already conducting pilot projects on the assignment of credit hours for physician office-based patient care quality-improvement activities [26].

Current e-prescribing systems cannot algorithmically recognize specific clinician knowledge gaps or intelligently ascertain when educational content is relevant to individual patients [21]. These limitations pose important challenges for the design and implementation of e-learning tools as part of e-prescribing systems. The critical step in integrating e-learning technologies into clinical decision support systems is achieving an adequate balance that ensures concise, context-appropriate information. Too much data or inappropriate information may discourage users. Context-sensitive e-learning materials and patient information, if available through hyperlinks, are more likely to be useful than drug information alone [21].

The other big challenge we face is ensuring physicians' competency in the use of the systems. Familiarity with e-prescribing and e-learning systems is not enough. Training and assessment are imperative, with simulated patients as a first step followed by demonstration of competency in using the system with actual patients.

In sum, e-prescribing enhanced by e-learning technologies can potentially assist clinicians by offering needed, just-in-time information at the point of care and guiding them through the individualization of drug-prescribing for their patients.

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Additional resources

The Leapfrog Group: <http://www.leapfroggroup.org/>

The eHealth Initiative: <http://www.ehealthinitiative.org/>

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 387-391.

Journal Discussion

Patent (and public health) pending

by Philip A. Perry, MSJ

Kesselheim AS, Avorn J. Biomedical patents and the public health. Is there a role for eminent domain? *JAMA*. 2006;295:434-437.

In a health crisis, such as a flu pandemic, prompt medical intervention by physicians and the public health community may save lives. Sometimes, however, the curative drugs are too expensive or there's just not enough to go around. Furthermore, physicians can't act when laws that protect the patent rights of pharmaceutical companies conflict with other laws that promote public health. Is there a mechanism that can resolve the conflict? Seeking a creative solution, the authors of this article—physician-lawyer Aaron S. Kesselheim, MD, JD, a clinical fellow in the Department of Medicine and Harvard School of Public Health and an associate physician at Brigham and Women's Hospital, and Jerry Avorn, MD, professor of medicine at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's—propose that the government's powers of eminent domain can and should be applied for the public good in serious health crises.

Eminent domain powers allow governments (local, state or federal) to buy property or take other actions in the name of the public good. The idea of just compensation for the exercise of eminent domain is written into the U.S. Constitution [1]. But while it has often been applied to real estate law, for example to build roads while compensating landowners for the sale (coerced or otherwise) of their property, eminent domain has not been a common legal instrument in the health care business.

A legal precedent retooled for health care

As the authors point out, however, the concept of eminent domain has broadened throughout U.S. legal history [2]. Eminent domain was used in 1948 to gain access to patented processes when that use of governmental power was established through the U.S. judicial code [3]. But it was a power seldom exercised, partly because of the weight of the free enterprise tradition that honored patents and innovation in U.S. commerce. In the tradition of hard bargaining, the power has been held in reserve, as a kind of ultimate weapon, while a favorable deal was cut between the patent holder and governmental authorities.

Kesselheim and Avorn propose that we apply the principle of eminent domain to the purchase of pharmaceutical or vaccine patents from private industry. In their scheme, a set of standards would be developed to determine when to invoke eminent domain. Possibly a standing committee of the U.S. Department of Health and Human Services would review requests for invoking the power and would try to work out a fair compensation deal for the patent owner. In some cases, a compromise might easily be reached with the company or individuals who hold the patent and intellectual property rights to a drug or device that's suddenly in demand. When time is money, or a matter of life or death, it's important to make sure that the mechanism for reaching a fair decision works quickly.

Eminent domain law requires fair compensation, so the public will eventually have to pay in some measure for what it needs. Economists have tried to estimate the cost of taking a drug patent and compensating the patent owner. In 1995, two Indiana State University economists, Robert C. Guell and Marvin Fischbaum, developed a fairly detailed theory involving a "market appeal" of commercial sales for a limited time to calculate just compensation prior to a government takeover [4]. Critics will probably object that there would not always be time for a market appeal, if, for example, an investigational drug proved useful against a pandemic that hit unexpectedly.

Kesselheim and Avorn make a good case that we need some kind of legal construct to protect the public in medical emergencies. Some have questioned whether it would be wise, or even constitutional, to invest the power of eminent domain in a committee of the Department of Health and Human Services, an agency of the executive branch. Legal challenges might tie up the courts for quite a while. And it certainly stacks the deck in favor of the government's side of the case.

Real world solutions hard to find

Real world experience demonstrates that the problem is a difficult one to solve. Both the AIDS epidemic and the more recent avian flu scare provide sobering examples. Pharmaceutical companies were assailed for their inhumanity in withholding drugs from needy patients, and governments were urged to force the companies to provide the AIDS cocktail free to the world's growing population of indigent patients, otherwise doomed. Avian flu raises the specter of deaths due to vaccine shortages or logistical failures of drug production.

During the anthrax scare, proposals in Congress floated the idea of government control of drug production by overriding patents on Bayer Corporation's antibiotic Cipro (ciprofloxacin hydrochloride) [5]. But the matter was dropped when the crisis passed with only a few serious cases. In the avian flu controversy of 2005, patent holder Roche did agree to allow generic Tamiflu to be produced by other companies during talks with U.S. lawmakers [6], but the agreement came only after considerable pressure was applied. Roche executives estimated that it would take generic manufacturers three years to gear up for any production, indicating that there's still a severe, unavoidable supply problem in a flu pandemic situation [7].

Meeting peak demand, corporate planners say, would require huge investments with an unacceptable risk of loss. Some sort of government guarantee as well as compulsory licensing might be necessary to build a big enough national stockpile of vaccine.

A Washington, D.C., councilman proposed an ordinance that would allow the city to take a drug company patent using its own powers of eminent domain. The reaction from a top drug industry lawyer was that it would never work. “Unwise, unworkable and unconstitutional,” said David Remes of Covington and Burling, an expert on patent law and an attorney representing the Pharmaceutical Research and Manufacturers of America [8].

One other limitation of the authors’ proposed legal instrument is that it stops at the U.S. borders. A pandemic would require an international solution. And the authors don’t really address the problem, which several other articles have raised, that the flu drugs are patented—and distributed—in only a handful of developed countries, so even if all were to nationalize the drug patents in an emergency many countries could still be without access to the drugs they needed [9]. One study, however, concluded that patents were not a serious barrier in Africa with reference to AIDS medications. Poverty and lack of public health infrastructure were much the greater problems [10].

Clearly, some compromise between commerce, government, and the public health is a prerequisite to successful medical interventions in these situations, whether local, national or international in scope. Yet eminent domain may be too disruptive. In legal theory, the knowledge that some “just compensation” is going to be forthcoming mitigates the disincentive to do research into and produce needed medications. But just compensation cannot match entrepreneurial returns from an exclusive patented blockbuster drug. If drug company innovation were to slow, then some other mechanism—such as increased government aid to drug company research and development efforts or guaranteed government contracts—would be needed to compensate for the inability of the private sector to meet a particular health threat. A current example is Washington’s \$1 billion support of manufacturers to accelerate their development of cell-based flu vaccine technology [11]. Application of eminent domain alone can’t be expected to meet all the possible competing needs of drug production and public health in an epidemic.

Ethics of denial of care

The market place has in effect denied care to many patients by pricing drugs out of their reach. The permanent solutions to this problem that have been proposed so far have been rejected—national health care, a group purchasing plan based on the federal government’s purchasing power, AIDS drug giveaways and so on. An awkward silence ensues for physicians, bioethicists and policy makers who take medical ethics seriously.

In their conclusion the authors note that it's difficult to decide when competing public goods have a claim on our sense of fairness. In this case, it's laid out as the good of "new drug development" versus the good of "access to lifesaving medicine." In so many cases the good of new drug development has seemingly won out, but the consequent inequities seem great. At what point does the fact that so many people cannot afford life-saving medications constitute an emergency in which the government should intervene for the good of the public?

Paradoxically, the more success there is in new drug development, the greater is the problem for the drug industry. William B. Schwartz, MD, pointed this out in "Life Without Disease," predicting that "a widening gap between what is medically possible and what is medically customary will create widespread conflicts between patients and health care providers, which will ultimately require resolution in legislatures and the courts" [12]. Constant demands for access and the lack of medications for indigent patients erode the image of medicine and the pharmaceutical industry. In the wake of the AIDS epidemic and in the face of avian flu and various threats real and imagined, pressure to find a better solution mounts.

Entering the courts on a case-by-case basis is not the most satisfactory alternative for the parties involved. If not eminent domain then some better, comprehensive legislative solution would seem to be the only road to a compromise that will balance competing commercial interests with urgent public health needs. All the more wonder that the situation the authors describe has been in stalemate for so long.

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 392-396.

Clinical Pearl

Clinical manifestations of vitamin B-12 deficiency

by Jennifer Reenan, MD

Type “vitamin B-12” into your favorite Internet search engine, and you’ll find an array of information and advertising sites touting various vague health benefits, including the “amazing” exercise-boosting ability of this complex compound. Despite its popularity as a general “energizer” for the body, mind and spirit, the evidence that vitamin B-12 should be taken either orally or parenterally by individuals who do not have a clinical diagnosis of deficiency is generally not convincing [1, 2].

One of the nine water-soluble vitamins, B-12, or cobalamin, has a chemical structure that is based on a corrin ring with a central metal ion (cobalt). Hailed as “nature’s most beautiful cofactor” [3] because of its unusual ruby red crystalline sheen, vitamin B-12 was discovered as a result of the work of Nobel-prize-winning Harvard scientists George Richards Minot and William Parry Murphy who were seeking a cure for pernicious anemia [4]. They discovered that a large diet of liver—up to a half-pound daily—induced dramatic improvement in both the clinical symptoms and hematologic lab results of their patients with pernicious anemia [4]. Subsequently, other scientists, including Dorothy Crowfoot Hodgkins, worked to purify, isolate and identify the structure of Minot and Murphy’s “antipernicious anaemia factor,” now known as vitamin B-12 [5].

Biochemical function

Vitamin B-12 is critical to the formation of mature erythrocytes, the synthesis of both DNA and RNA and myelin production, particularly in the spinal cord. Its main biochemical function is as a cofactor (in the form of methylcobalamin) for methionine synthase in the enzymatically driven reaction leading to the synthesis of the amino acid methionine from homocysteine. Methionine synthase also drives the conversion of 5-methyl tetrahydrofolate to tetrahydrofolate, the active form of folate that is necessary for the *de novo* synthesis of purine nucleotides (and therefore DNA and RNA) [6]. Methionine itself is part of the chemical process involved in the creation of S-adenosylmethionine, a substance critical to myelin formation and the methylation of DNA and RNA [7].

Another co-enzyme form of vitamin B-12, 5-deoxyadenosylcobalamin, serves as a cofactor for methylmalonyl-CoA mutase, the enzyme that leads to the synthesis of

succinyl Co-A, an intermediate of citric acid and a precursor of porphyrin (and therefore, heme) synthesis [8]. Succinyl-CoA is also critical to the catabolism of some fatty acids and the production of energy [8].

Physiology and metabolism

Found primarily in meats (especially liver), eggs, poultry, shellfish and milk, dietary vitamin B-12 is cleaved from its food source by the highly acidic environment of the stomach. It binds briefly to a gastric R binder protein before being freed by pancreatic peptidases in the duodenum and jejunum. Once free, the vitamin forms a complex with intrinsic factor, a chemical produced by gastric parietal cells [8].

This vitamin B-12-intrinsic factor complex is the chief mechanism by which the vitamin is absorbed across the distal ileal mucosa via an energy-dependent process. Another method of absorption believed to be independent of intrinsic factor may be capable of transporting a small amount (approximately 1 percent) of orally ingested vitamin B-12 into the mucosal cells [9]. Transcobalamin in the cells picks up the free vitamin after it has been released from its intrinsic factor complex and transports it through the portal circulation to the liver, where the majority of the body's vitamin B-12 is stored.

Pathophysiology: vitamin B-12 deficiency

Low levels of serum vitamin B-12 are of particular concern to the elderly, with several studies identifying a deficiency in up to 15 percent of the over-65 population [10, 11], perhaps related to overuse of gastric antacid agents [12]. Alcoholics and individuals who consume strict vegan or vegetarian diets are also at risk. Serum cobalamin levels can be ordered for initial screening, with levels less than 400 pg/mL (295 pmol/L) being of possible concern [12]. If serum cobalamin levels are suspicious, serum or urine methylmalonic acid and homocysteine levels can confirm the deficiency [12].

Megaloblastic anemia. If vitamin B-12 is not absorbed in the ileum due to a nutritional deficit or malabsorption-related problem (e.g., pernicious anemia, gastrectomy, small intestine disorders), methionine synthase activity slows down, reducing the rate of conversion of methyltetrahydrofolate to tetrahydrofolate, the active form of folate.

Thus vitamin B-12 deficiency effectively induces a functional folate deficiency, with significant “methylfolate trapping” [6], resulting in impaired DNA and RNA synthesis and the production of “large, immature, hemoglobin-poor red blood cells” with an elevated mean corpuscular volume and an elevated mean corpuscular hemoglobin concentration [13]. According to the “Cecil Textbook of Medicine,” “methylfolate trapping explains why cobalamin deficiency and folate deficiency produce indistinguishable hematologic abnormalities” [6].

In the classic vitamin B-12 deficiency disease, pernicious anemia, an autoimmune process leads to decreased intrinsic factor production in the gastric parietal cells.

Traditionally, pernicious anemia was diagnosed by a Schilling test using radio-labeled vitamin B-12 to detect impaired intestinal absorption [12].

Neuropsychiatric symptoms. White matter and axonal degeneration may be seen in the spinal cord, cerebrum or peripheral nerves of individuals suffering from chronic (5-10 years) vitamin B-12 deficiency [14, 15]. Neurologic and psychiatric abnormalities associated with vitamin B-12 deficiency may not reverse, despite proper supplementation [8]. Symptoms such as numbness and paresthesias in the extremities, loss of position and vibratory sensation, difficulty walking, depression and irritability, diminished cognitive function (including memory impairment), and psychosis may be observed even in the absence of hematologic disease [8, 15].

Gastrointestinal symptoms. Glossitis, cheilosis, anorexia, diarrhea, constipation and weight loss have been associated with vitamin B-12 deficiency.

Cardiovascular effects. One of the major findings of the Framingham Heart Study was that high levels of plasma homocysteine may be associated with an increased risk of cardiovascular disease, including stroke, coronary artery disease and peripheral artery disease [16]. While folic acid and vitamin B-12 (to a lesser extent) are both effective at reducing homocysteine levels, the evidence so far does not suggest that folic acid and vitamin B-12 supplements taken together or separately will reduce the risk of major vascular events, including the incidence of death from myocardial infarction and stroke [17-19]. The HOPE 2 investigators recently explained this apparent discordance by suggesting that “homocysteine could be a marker, but not a cause, of vascular disease” [17].

Recommended intake and treatment

Where serum levels of vitamin B-12 are adequate, extra vitamin B-12 is unlikely to be the direct cause of any improvement in nonspecific symptoms of fatigue and low energy. Lawhorne and Ringdahl observed that “the efficacy perceived by the patient [is] more likely related to the support, reassurance, and hands-on care provided by the physician rather than the injection that [gives] the visit credibility in the eyes of the patient’s family and community” [1]. While such injections may have once been considered medically, or even psychologically, appropriate, use of vitamin B-12 as a “tonic” for fatigue, weakness or muscle aches in the absence of either a real deficiency or a definitive randomized, double blind, placebo-controlled trial that establishes benefit must be considered unnecessary.

The daily requirement of dietary vitamin B-12 is 2.4 mcg for most adults [20]. Despite the prevalence of vitamin B-12 deficiency in the geriatric population, there is no current agreement on whether or not screening should be universal for older adults who do not possess risk factors [15]. There is also “no accepted screening protocol for vitamin B-12 deficiency” [15]. As mentioned above, a serum B-12 is generally the first-line lab screen. If the serum B-12 level is borderline, a serum homocysteine or serum methylmalonic acid test can be ordered for more diagnostic specificity. For those who do require supplementation or replacement due to

insufficient vitamin B-12, oral or intramuscular therapy should be given, usually at levels well above the daily requirement [12, 15].

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 397-402.

Case in Health Law

Neurontin and off-label marketing

by Christian J. Krautkramer

When the Food and Drug Administration approves a drug for use in the general population, it does so with specific labeling. This labeling usually comes about after many years of study, culminating in clinical trials conducted with individuals who have the condition the drug is designed to treat. If deemed safe and effective, the drug is indicated as an approved treatment for a particular condition, sometimes within a specific population.

Off-label prescribing and marketing

Physicians are allowed to prescribe any drug they see fit to treat a patient's ailment [1]. This includes so-called "off-label" prescribing, that is, prescribing for a use not indicated by the FDA. Such prescribing generally occurs when a drug is thought to have therapeutic benefit (usually because of repeated common usage) but has not been labeled for treatment of a given ailment for reasons of cost, proprietary jurisdiction or yet-to-be-finalized data. Perhaps the best known example is aspirin, which was recommended off-label for treatment of hypertension and angina until 1998 when the FDA labeled it for such treatment [2]. And surveys indicate that most physicians who treat cancer patients have prescribed drugs off-label as tumor-reducing therapy [3]. The federal government has noted that this widely established medical practice is consistent with the best aspects of medical care when the physician has carefully weighed the risks and benefits of such prescribing [4].

Although off-label prescribing of a drug is permissible, the off-label *marketing* of that drug is not, and it is within the purview of the FDA to regulate such marketing. Under several provisions of the Food, Drug, and Cosmetic Act, a company must specify all intended uses in its new drug application to the FDA [5]. Once approved, the drug may not be legally marketed or promoted for any use not specified in the application and approved by the FDA. Off-label marketing is seen by many legal experts and ethicists as a practice fraught with the potential for abuse. Savvy drug manufacturers would be able to convince physicians to prescribe their drug for an indication where, at a minimum, a better drug was available and, at a maximum, the drug had no legitimate claim to its purported therapeutic effects.

Perhaps no case is better known for the dangers of off-label promotion than that of Neurontin. When the FDA granted approval to Parke-Davis for its drug Neurontin

(gabapentin), it was originally labeled for use as an adjunctive therapy for epileptic seizures (that is, not for use by itself but as an add-on drug to strengthen primary anti-epilepsy pharmacotherapy). Some limited studies, however, showed that Neurontin might also help individuals with a variety of mental health disorders (bipolar and attention-deficit/hyperactive disorders [ADHD] and alcohol withdrawal), restless leg syndrome, migraine headaches and other pain disorders.

Marketing

In order to boost sales of the drug, Parke-Davis engaged in what would later be judged to be illegal off-label marketing practices, pushing the drug to physicians for myriad uses for which it had not originally been approved. The details of these practices were revealed in the aftermath of a lawsuit brought by a former Parke-Davis employee under the federal False Claim Act (FCA), the government's primary legal tool for preventing waste, fraud and abuse by businesses. The FCA combats such improprieties through several mechanisms including:

1. Making persons liable for criminal prosecution who knowingly present or cause to be presented to an officer or employee of the United States Government false or fraudulent claims for payment or approval, or
2. Making persons liable for prosecution who knowingly make, use or cause to be made or used, false records or statements to get false or fraudulent claims paid or approved by the federal government [6].

Individuals in violation of the FCA are responsible, under law, for a civil penalty plus three times the amount of damages which the government sustains because of the act of that person. Thus, the FCA creates an incentive for private parties (or "relators") who learn of criminal activity to bring legal action on behalf of the government. For each violation of the FCA, a successful relator collects a large percentage of the civil penalty and monetary damages owed to the government.

The case against Neurontin

The relator in the Neurontin case was David Franklin, MD, a microbiologist employed by Parke-Davis as a "medical liaison." Franklin and several other liaisons, most of whom had medical or graduate bioscience degrees, were hired to answer doctors' technical questions about Neurontin. Medical liaisons are not considered sales representatives by pharmaceutical companies, and they are forbidden under law to talk to doctors about off-label uses unless the doctor has a specific question. Franklin, however, said he was trained as part of a plan created by Parke-Davis executives to sell Neurontin for a variety of conditions for which it was not labeled, including migraines, manic-depression and ADHD. Such training focused on earning doctors' trust and then providing them information about off-label uses for Neurontin.

Franklin stated that within a few weeks of starting his medical liaison job, he realized that he had become a major part of a campaign to market Neurontin illegally for more than a dozen uses for which it was not FDA-labeled [7]. He decided to bring

suit through the whistleblower language in the FCA. The complaint, based on Franklin's five months with the company, alleged that his former employer engaged in a campaign of false and misleading statements intended to defraud the federal government of hundreds of millions of dollars through the needless purchase of Neurontin for Medicaid beneficiaries [8].

In his complaint, Franklin described a "publication strategy" in which Parke-Davis allegedly used and then surpassed the limited leeway it had to promote off-label uses of Neurontin. [9] First, the company sought to take advantage of a pre-Food and Drug Administration Modernization Act of 1997 regulation that permitted manufacturers to distribute publications describing off-label uses of FDA-approved drugs so long as the publications were produced by third parties. For example, the company allegedly hired non-physician technical writers to ghostwrite articles for medical journals and then paid actual specialists to sign as the articles' authors. Physicians were also paid to conduct meaningless clinical trials of Neurontin's off-label uses with cohort sizes too small for any conclusive results to be found [10].

Franklin also claimed that Parke-Davis knew that it was inappropriate to use medical liaisons as salespersons. Before extending the job offer, the company asked Franklin whether he had difficulty working in gray areas or bending rules, and during a training session he was warned that "under no circumstances should any information about off-label uses be put in writing" [8]. After taking the job, Franklin ran into situations in which medical liaisons were introduced as academics "on-leave" from their teaching or research to lend credibility to their sales pitch.

When Franklin brought concerns about the marketing practices to his superiors, he was put off. A physician he was "pitching" showed Franklin an article stating that Neurontin had worsened the behavior of a child with attention deficit disorder. When he later showed the article to his boss, Franklin said that his boss had laughed and said, "Well, the doctor should not have been using the stuff off label anyway" [7].

Concluding his allegations, Franklin observed that

one-quarter to one-third of all Neurontin prescriptions in the United States were paid for by the Medicaid program....[Parke-Davis] knew that off-label prescriptions for Neurontin were ineligible for Medicaid reimbursement and that its activities would, in fact, cause numerous ineligible prescriptions to be submitted to Medicaid [8].

Medicaid fraud was the linchpin for this case [9]. Medicaid can generally only be used for covered outpatient drugs and not for off-label use unless the drug is included in one of the identified drug compendia [11]. On behalf of the United States government, therefore, Franklin charged Parke-Davis with causing pharmacists, doctors and patients to request and receive reimbursement for uses of Neurontin not covered by the Medicaid program.

While the case was pending, Pfizer [12]—which acquired Parke-Davis in 2000—said that it was not aware of any false statements about the off-label use of Neurontin made by Parke-Davis employees and that any statements would have been made well before it acquired the company. In 2003, Neurontin accounted for \$2.3 billion of Pfizer’s sales and was one of the company’s top-selling drugs. Pfizer said in court papers that more than 78 percent of Neurontin prescriptions in 2000 were written for unapproved uses.

Settlement

In 2004, after eight years in the legal system, Pfizer agreed to plead guilty to charges of falsely marketing Neurontin and defrauding the federal government. [13] As part of the terms of its plea, Pfizer:

1. Acknowledged it had misbranded Neurontin by failing to provide adequate directions for use and by introduction into interstate commerce of an unapproved new drug;
2. Settled criminal liabilities incurred by Medicaid fraud to the federal government due to violation of the FCA;
3. Settled civil liabilities incurred by Medicaid fraud to all 50 state governments and the District of Columbia;
4. Settled civil liabilities incurred by consumer harm to all 50 state governments and the District of Columbia;
5. Set up a corporate compliance program to ensure that changes in marketing practices that Pfizer made after it acquired Warner-Lambert are effective.

The criminal and civil liabilities, in total, equaled \$430 million, including \$240 million in criminal fines, the second largest ever imposed in a health care fraud prosecution.

Because of the whistleblower incentive in the FCA, Franklin and his attorneys shared in the civil award and received more than \$26 million.

Conclusion

The case of Neurontin has brought increased exposure to pharmaceutical company marketing practices. Although off-label prescribing continues to be a valued part of clinical practice, the marketing of drugs off-label is seen as a corruptive practice that threatens the integrity of medicine.

Since this case was brought, Neurontin was approved by the FDA for pain related to shingles, one of the off-label prescriptions for which it was not indicated at the time of the suit. But while physicians certainly have a responsibility not to pay attention to off-label marketing, it is the responsibility of the pharmaceutical industry to create an environment where such practices are not present to influence physicians.

Whether the warning of the Neurontin case will stop off-label marketing in the future or simply spur pharmaceutical companies to come up with more creative ways to promote their drugs remains to be seen.

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Disclosure: The AMA received a grant to develop curriculum on ethical prescribing practices for medical students, residents and physicians funded by the settlement of the Neurontin suit and distributed by the Attorney General Consumer and Prescriber Grant Program. The author of this article and a Virtual Mentor editor are helping develop the curriculum, but neither is a recipient of grant funds.

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 403-406.

Policy Forum

Reputation, gatekeeping and the politics of post-marketing drug regulation

by Daniel Carpenter, PhD

The withdrawal of Merck's Vioxx (rofecoxib) in September 2004 has occasioned a series of discussions about the institutions of pharmaceutical regulation in the United States and around the globe. The U.S. Senate Finance Committee, under the chairmanship of Charles Grassley (R-Iowa), has held several high-profile hearings on the issue. This past April, the General Accounting Office (GAO) issued a report that was highly critical of existing policy and suggested several reforms, including expanded FDA authority to require that post-market studies be carried out by drug companies [1, 2]. These ongoing policy initiatives have been accompanied by proposals from prominent medical academics and medical journal editors for the creation of a drug safety office or commission that is independent of the FDA, or at least of its drug approval divisions [3-6].

The current dilemma—and its embedment in the conflict between pre-market approval and post-market surveillance—has a long history. For several decades now, critics and observers of U.S. pharmaceutical regulation have singled out the post-marketing surveillance system for complaints. And their conclusions, while varied in some respects, have often revisited the perceived conflict between pre-market and post-market processes. Consider for example the late 1970s and early 1980s. In September 1979, the Drug Regulation Reform Act of 1979—which would have equipped the FDA with authority to require post-marketing surveillance studies for up to five years after approval and would also have loosened the standards for post-market withdrawal—passed the Senate (it would never pass the House and hence never became law). One year later, the Joint Commission on Prescription Drug Use proposed a “national Center for Drug Surveillance (CDS)” —an agency independent of the FDA’s new drug review divisions—that would “perform and encourage research into drug effects” [7-9].

The promise and the perils of efforts to reform post-marketing regulation are linked to two related and deeply patterned features of U.S. pharmaceutical regulation. The first is organizational reputation—one of the most powerful forces animating and constraining government agencies, indeed, any complex organization. The second force is gatekeeping—the fact that the FDA’s primary power over prescription drugs is exercised before the drugs reach the market.

1. *Organizational reputation and post-market surveillance.* The FDA's public reputation as patient and consumer protector in the American health care system is a powerful one, and the incentives for its protection consciously and unconsciously influence much regulatory behavior. Indeed, while the usual conflict of interest debates in drug regulation pertain to advisory committee representatives who have received industry money, the vesting of authority over post-marketing surveillance in the Office of New Drugs creates a different but no less powerful conflict of interest that current policy does not recognize. The very office of the FDA that approves new drugs—and which therefore has the least reputational incentives to revisit its past approval decisions—is also the office with legal authority over post-marketing [10]. As the GAO has recognized, the FDA's Office of Drug Safety, which houses the agency's epidemiologists and its major capacities for post-market surveillance, is only a weak consultant to the Office of New Drugs.

It is perhaps audacious to claim, and certainly difficult to prove, that reputational incentives weaken the Office of New Drugs' willingness to scrutinize drugs that have already been approved. Yet characterizations to this effect have been with us for 50 years—from medical reviewer John Nestor's 1963 testimony before Congress that FDA medical reviewers were discouraged from revisiting past approval decisions, to David Graham's lament that “the new drug reviewing division that approved the drug in the first place and that regards it as its own child, typically proves to be the single greatest obstacle to effectively dealing with serious drug safety issues” [11]. FDA observers and FDA officials themselves have consistently pointed to institutional reluctance to revisit past decisions [11, 12]. One need not agree entirely with either Nestor's or Graham's broader arguments to see the plausibility of their depictions of the FDA.

2. *Gatekeeping and the asymmetry of power.* The New Drug Application (NDA) is the central document, and in some ways the central procedural institution, of U.S. pharmaceutical regulation. It is the authority of the FDA to render a company's NDA effective that gives the agency gatekeeping power over the U.S. health care system. Once a drug is approved, much of the FDA's power over pharmaceutical companies is lost, and so are the incentives of pharmaceutical companies to behave in strict conformity with FDA wishes. When the FDA wishes a company to tweak a Phase II or Phase III clinical trial, or to gather additional information on a drug *before* an NDA is approved, pharmaceutical sponsors respond quickly and completely. Once the drug is “past the gate,” however, this behavior changes. The best example of this lies in the low initiation and completion rate of Phase IV studies. Of the 1,191 Phase IV post-marketing commitments that had been made as of Sept. 30, 2004, 68 percent had not been started. [13, 14].

As is it is currently endowed, the FDA can do little about such patterns. The set of punishments available to the FDA is brute, not nuanced. Faced with a noncompliant firm that refuses to honor its Phase IV commitments, the FDA cannot issue fines, restrict advertising or impose any administrative penalty save that of suspending the company's NDA. The political incentives weighing against NDA suspension—as

well as the punishment this delivers to patients and their physicians—render Phase IV commitments essentially unenforceable.

I have no confident predictions to offer regarding the future of policy reforms. As long as reputational incentives govern the FDA, there will be conflict between those who approve drugs and those who scrutinize those same drugs once they have entered the market. And as long as the FDA's authority remains weighted toward pre-market approval, the agency will have a difficult time inducing optimal behavior by firms. The United States will likely remain mired in its current dilemmas, without effective policy options to combat post-market safety troubles.

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was hired, after joining the organization I found that any medical opinion that raised issues that involved reappraisal of past decisions, past policies, or past commitments to the pharmaceutical industry would be challenged—not in a healthy scientific atmosphere, but, rather, with indifference, disapproval, or even hostility.” Later in the same hearing, Nestor remarks that “What the problem seemed to be was that in making present decisions, it was sort of sacrosanct situation that we were not to question decisions made in the past.” See Interagency Coordination in Drug Research and Regulation. *Hearings Before the Subcommittee on Reorganization and International Organizations of the Committee on Government Operations. Part 3, The Bureau of Medicine in the Food and Drug Administration.* US Senate, 89th Congress, 1st Sess, (March 20, 1963):783, 790.

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Research for this article was funded by the National Science Foundation and an Investigator Award in Health Policy Research from the Robert Wood Johnson Foundation. Professor Carpenter neither seeks nor accepts research funding or any other form of compensation from the FDA or from any commercial entity that sponsors product applications to the FDA.

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 407-411.

Medicine and Society

Direct-to-consumer drug ads, patient autonomy and the responsible exercise of power

by Richard L. Kravitz, MD, MSPH, and Jodi Halpern, MD, PhD

It has been nine years since the Food and Drug Administration relaxed its interpretation of the 1962 Kefauver-Harris Amendments and unleashed a torrent of direct-to-consumer (DTC) advertisements in print, on radio and on television [1]. Cumulative spending on DTC advertising since 1997 approaches \$20 billion, with \$4.5 billion reported in 2004 alone. Though nonproprietary data are sparse, one can safely assume that pharmaceutical companies would not make investments of this magnitude without achieving consistently good returns.

The two sides in the DTC advertising debate line up in predictable ways [2]. Critics argue that DTC motivates patients to seek unnecessary and expensive treatments for trivial conditions, engenders discord in the patient-physician relationship and distracts doctors from their principal job of diagnosing and treating illness. That thinking has changed, and since 1997 industry spokespeople and their academic defenders argue that DTC advertising encourages treatment seeking by those who might otherwise go undiagnosed, delivers good educational value and, in any case, qualifies as protected speech under the First Amendment. While pharmaceutical companies are most clearly empowered by DTC advertising, defenders offer an ethical argument that does seem to trump all others: patients have a *right* to health care information and no one—not doctors, not consumer advocates, not the Food and Drug Administration—should interfere with patients' unrestricted access to that information. Anything else smacks of paternalism and *that* went out of fashion a long time ago.

Lost in the debate is whether, along with rights, patients have any duties as health care consumers. This is a tricky matter not often considered by medical ethicists. The possibility that patients have duties as well as rights comes up in discussion of the covenant that serves the moral and legal foundation of the patient-physician relationship [3]. As part of this covenant, for example, physicians are enjoined to place patients' welfare first. Patients commit to disclosing their symptoms and past histories, negotiating and adhering to mutually acceptable treatment plans, and attending follow-up appointments. Medico-legal doctrine tacitly acknowledges the concept of parallel rights and duties by absolving physicians of malpractice if the cause of injury is the patient's repeated failure to adhere to the agreed-upon

treatment plan. Fundamentally then, patients' covenantal duties derive from a general principle of respect for persons—in this case, the person of the doctor and, by extension, other patients under that physician's care. Put more plainly, patients shouldn't demand inappropriate medical treatment because to do so devalues medical care and also wastes resources that are needed for other patients.

Surveys conducted in communities and in clinical settings indicate that direct-to-consumer advertising motivates consumers to seek care and request prescriptions [2, 4, 5]. Until recently, however, there was scant evidence addressing the effect of such requests on physician behavior. In a recent study, investigators trained two groups of actors ("standardized patients" or SPs), one to portray patients with major depression of moderate severity, which is a serious condition requiring treatment, referral or close follow-up, and the other to portray patients with an adjustment disorder, a less serious condition for which supportive counseling and watchful waiting might suffice [6]. SPs were randomly assigned to visit 152 primary-care physicians in three U.S. cities (298 visits in all). Within each of the two main groups, one-third of the actresses (all non-Hispanic, white, middle-aged women) mentioned a TV advertisement and made a brand-specific request for Paxil (paroxetine); another one-third made a general request for "medicine that might help"; and the rest made no request.

There were two main findings. First, among SPs presenting with major depression, those who made no request had only a 56 percent chance of receiving high-quality initial care (antidepressant prescription, mental health referral or close follow-up). In contrast, SPs who made a brand-specific or general request for medication were treated to this standard in over 90 percent of visits. Second, among SPs presenting with adjustment disorder, the proportion receiving an antidepressant prescription was 55 percent if a brand-specific request was made, 39 percent if a general request was made and 10 percent if no request was made.

One ethically significant result of this research is the impression that physicians tend to comply with patients' requests, at least in the gray areas of clinical practice where clear-cut guidelines are scant [7]. This brings into relief an often hidden foundation of the patient-physician relationship. Just as patients expect physicians to recognize their right to participate in medical decision making, *physicians depend on patients to recognize the clinical judgment and professionalism that they (physicians) bring to the encounter*. Social theorists show how patients actually have the power to grant physicians their status as professionals or to refrain from doing so. Patients play a voluntary role by allowing doctors the authority to probe their bodies and ask private questions, and this in fact defines the doctor's role. Without patient acknowledgment of the propriety of doctors doing this, such exams could never take place [8-11].

Imagine a world in which patients trust television advertisements more than they trust physicians and insist that their doctors have nothing to offer them except cheerful compliance with their requests. In such a world, patients would shuttle between their televisions, on which they would watch DTC ads, their physicians'

offices, where they would present a shopping list of “needed” drugs, and their computers, on which they would order pharmaceuticals directly from the Internet. The very involvement of doctors in care might soon be rendered irrelevant. Insofar as patients do benefit from physicians who are prepared to render trustworthy advice, they have a crucial responsibility to sustain the value of clinical judgment. That responsibility is expressed in seeking to engage in genuine dialogue about treatment efficacy and outcomes. Though clinically worthwhile, such conversations should not promise to satisfy all consumer desires.

Importantly, this model of mutual regard in no way limits patient autonomy. Just as doctors need not comply with their patient’s requests, patients need not follow their physician’s advice. They do, however, need to be informed. This requires access to high quality information. DTC advertising delivers relatively little educational value [12]. One solution is for drug company consortia to fund public service announcements that would not only educate patients about specific problems but also help them formulate good questions for their physicians such as, “How many people with my problem are helped by this medication?” and “What are the risks and benefits?” Health care organizations would have the reciprocal obligation to structure patient visits so that doctors are not so time pressured that they reflexively comply with requests rather than engage in educational dialogue [13].

Over time, patients should also be educated to see the public health implications of their DTC advertising-related demands: *seeking unnecessary prescriptions can result, indirectly but ineluctably, in harm to others*. One can imagine several mechanisms. First, overuse of a drug might make it less effective for future users; antibiotic resistance comes to mind. Second, inappropriate consumption of a scarce drug (e.g., ciprofloxacin during the 2001 anthrax scare) could limit the drug’s availability to others who have greater clinical need. Third, the provision of unnecessary medical services (including expensive, unindicated, brand-name prescription drugs) strips resources from more effective forms of care. The little-noticed victim of clinically unwarranted prescribing is the patient who could have benefited from an effective treatment but cannot gain access to it because society’s resources have been exhausted at the hands of profligate consumers and their co-conspirators in the medical-industrial complex [14].

Directly educating patients about medicines, preferably through public service campaigns, not only respects patient autonomy but promises to promote better health. Patients with chronic illnesses who become actively involved in their medical care tend to achieve better health outcomes [15]. Seeing a DTC advertisement, making an appointment and asking the doctor about the merits of a new treatment are among the behaviors that studies would classify as “active.” Overall, patients benefit most from a system that respects their active role. But such a system need not sacrifice the value of physician-patient engagement that is genuinely educational and guiding. Protecting the time for and the value of such interactions, however, depends crucially on patients responsibly exercising their prerogatives by refraining from making requests willy-nilly. By acting as responsible partners rather than willing

victims of commercial manipulation, patients can ensure that even when they don't get what they want, they get what they need.

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Related article

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 412-415.

Op-Ed

“This may sting a bit”: cutting CME’s ties to pharma

by Adriane Fugh-Berman, MD, and Sharon Batt, MA

A recent proposal to address conflicts of interest in academic medical centers suggested that industry support of continuing medical education (CME) activities should be limited to contributions to a central fund that would disburse the money to programs accredited by the Accreditation Council for Continuing Medical Education. The authors of the proposal reason that this arrangement would “permit the central repository and the ultimate recipients of funds to remain free from influence by any one donor company” [1]. We would go further: only CME activities that are entirely free of pharmaceutical industry funding should qualify as education.

The superficially appealing but fundamentally flawed “pooled donor” solution seeks to preserve access to pharmaceutical funding while restraining donor influence on educational content. But the assumption that blending competing conflicts somehow cancels the conflicts out does not bear close examination.

Medicine is a profession, and pharmaceutical marketing is a business. The obligation of physicians is to patients; the obligation of a pharmaceutical company is to shareholders. The interests of medicine and pharmaceutical manufacturers are not congruent. The collegial relationship between the two would undoubtedly cool were physician signatures not a prerequisite for prescription drug sales. Physicians are considered by the industry to be a barrier to surmount; in an article called “A Medical Publisher Reminds Us: Don’t Forget the Gatekeepers,” aimed at the pharmaceutical industry, the author tells drug execs that prescribers “stand between the consumer and your drug” [2].

Gifts have been shown to create obligations. Indebtedness to pharmaceutical manufacturers as an industry rather than to individual companies merely renders the obligation less visible—and more decorous, perhaps. It is in the interests of all pharmaceutical companies to engage in disease mongering by expanding diagnostic categories so more people are eligible for drug treatment and to convince physicians that drugs are the only viable therapeutic options. While physicians who receive CME funded by a corporate coalition may not be subjected to presentations promoting specific drugs, the “Drugs-R-Us” model of medicine is still reinforced. Diet, exercise and other nonpharmacologic approaches to disease prevention and treatment will continue to be marginalized.

Continuing medical education should not be equated with sales; industry-funded CME is a precursor to sales. Pharmaceutical company sponsorship of CME is designed to create or reinforce perceptions about disease that increase prescriptions for target classes of drugs. For example, speakers may be hired to deliver the messages that disease X is epidemic, underdiagnosed and debilitating and that effective treatments are available. Nothing there to raise eyebrows; for industry, the most successful CME events appear completely objective. The sponsor's drugs are not emphasized because physicians reject educational presentations that seem to be advertisements. In fact, speakers who hope to get more industry engagements by hawking the sponsor's drugs will find themselves dumped from the CME circuit instead. Speakers who sound like drug reps alienate physician audiences and thus work against industry interests. Pharmaceutical company-sponsored CME is designed to increase the receptivity of physicians to prescribe more of a target group of drugs. It is then up to the sales staff of competing drug companies to determine the market share of drugs within that group.

Rather than attempting to devise ethical ways for physicians to maintain their dependence on industry-funded CME, it is time to search for true alternatives. The education of physicians should be funded by physicians, not by a third party whose profits are directly related to prescribing behavior. Weaning CME from the industry breast is like striving to meet our energy needs without oil—tough but necessary. The presumption that pharmaceutical manufacturers' funds are necessary for CME permeates medical culture. The AMA itself takes industry funds. In 2000, in what Carl Elliott has called a “stunningly inept” decision, the AMA accepted pharmaceutical company co-funding for a campaign to provide doctors with ethical guidelines regarding gifts from industry [3].

In 2004, more than \$2 billion was spent on CME; pharmaceutical manufacturers paid for more than half of that sum. Firms that manufacture FDA-regulated products (primarily pharmaceuticals) provided three-quarters (74.7 percent) of the income of medical education and communication companies (MECCs). CME provided by medical schools is almost equally reliant on the pharmaceutical industry, which provides almost two-thirds (63.8 percent) of CME income to medical schools [4].

This distinction between MECCs and medical schools may blur further with the advent of academic-industry partnerships. One example is Engaging Minds, a joint venture among University of Medicine and Dentistry of New Jersey (UMDNJ), Pegasus Healthcare International in Montreal, and Saber Communications in New York [5]. Until it was removed recently, a brochure titled “A University-Industry Partnership in Education” on the Web site of UMDNJ's Center for Outreach and Continuing Education (CCOE) boasted that “CCOE and UMDMJ faculty can advise, assist, and advocate to propose and position educational activities for product awareness, acceptance, and utilization” [6].

Pharmaceutical companies have good reason to value CME. A 2004 survey of 4,600 physicians, conducted by Verispan, found that educational seminars ranked highest

in effective sales tactics [7]. A smaller industry poll of 237 physicians in the fall of 2005 also found that physicians (at least those attending CME events where the survey was done) rated CME to be their most valued information source, followed closely by medical journals and peer interaction [8].

It is not as though physicians cannot afford to pay for CME. In the U.S. physicians and surgeons have the highest median income of all workers [9]. Expenses for CME courses are tax-deductible, and free CME opportunities are regularly offered through federal agencies. A 2004 editorial in the Canadian Medical Association Journal asks pointedly, “does the harm from allowing CME to be orchestrated by pharmaceutical companies outweigh the benefits of being able to offer it at a greatly subsidized cost, or free, to physicians?... Playing second fiddle in the big-pharma orchestra is not leadership” [10].

Several years ago, the Mahatma Gandhi Institute of Medical Sciences, a rural medical college in Sevagram, Maharashtra, India, decided to refuse drug industry support for any conferences, seminars or workshops, thus becoming “the first medical institute in the country to keep [the] drug industry away from medical education” [11]. Surely, if a rural medical college in India can afford to scorn the bribes of pharma, one medical school in the US could show the same leadership?

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Disclosure: Adriane Fugh-Berman has received speaking fees from Medical Education Communication Companies (MECCs).

Related article

[Independence in continuing medical education](#), June 2006

[Commercial support for continuing education](#), July 2003.

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 416-419.

Op-Ed

Independence in continuing medical education

by Murray Kopelow, MD, MSC, FRCPC

Approximately 70 percent of the physicians in the United States are required by their state medical licensing boards to participate annually in formal, structured continuing medical educational activities to meet licensure requirements [1]. Among the details of these regulations are requirements that the education activity be designated for credit according to standards described within the American Medical Association's Physician Recognition Award [2] and provided by an institution or organization accredited by the Accreditation Council for Continuing Medical Education (ACCME) [3].

A large proportion of the funding for this accredited continuing medical education (CME) comes from commercial interests (proprietary entities like pharmaceutical companies or biomedical device manufacturers that produce health care goods and services consumed by, or used on, patients). ACCME-accredited providers use approximately \$1 billion of direct or in-kind support from commercial interests to finance their accredited CME activities [4].

Accredited CME is not the only interaction with physicians that commercial interests fund. Among their other activities, they fund nonaccredited organizations to create live events or printed materials for physicians using the same formats as those used by CME, but these are designed and offered as promotion for their specific products. In medical education in the U.S., compliance with the ACCME Standards for Commercial Support distinguishes approved, independent CME from activities that are promotion events created by commercial interests [5].

The Standards for Commercial Support of Continuing Medical Education include "Standards for Independence in CME," which are the medical profession's mechanism to manage the boundary issues created by the coexistence of continuing medical education with commercial support, commercial interests, promotion and advertising [6].

Standards for independence in CME

The standards address independence, identifying and resolving personal conflicts of interest, management of commercial support, separation of promotion from education, and ensuring improvements in health care.

Standard 1—*independence*—requires the CME provider to ensure that critical decisions involved in the planning of a CME activity are made free of the control of a commercial interest. Specifically these decision points are identification of CME needs, determination of educational objectives, selection and presentation of content, selection of all persons and organizations that will be in a position to control the content of the CME, selection of educational methods, and evaluation of the activity. So as to not undermine this independence, ACCME stipulates that a commercial interest cannot take the role of nonaccredited partner in a joint sponsorship relationship that has been established to design and present a CME activity.

Standard 2—*resolution of personal conflicts of interest*—is new to the 2004 updated “Standards for Commercial Support” and undergirds the independence in CME. To be compliant with this standard the provider must be able to show that everyone who is in a position to control the content of an education activity has disclosed to the provider all relevant financial relationships with any commercial entity. The ACCME defines “relevant financial relationships” as financial relationships in any amount occurring within the past 12 months that create a conflict of interest [6]. The provider must take the steps necessary to identify and resolve all conflicts of interest prior to delivery of the education activity to learners. Disclosure is critical to being able to identify and resolve any conflicts of interest. Therefore, an individual who refuses to disclose relevant financial relationships must be disqualified from being a planning committee member, a teacher or an author of CME and cannot have control of or responsibility for the development, management, presentation or evaluation of a CME activity.

Standard 3—*appropriate use of commercial support*—ensures that commercial support is spent on the costs of the education. The provider may not use commercial support to pay for travel, lodging, honoraria or personal expenses for nonteacher or nonauthor participants of a CME activity. This standard requires the presence of written agreements that document source of the funds, the terms of support, that funds are not used to pay the learners’ personal expenses and that the provider can produce an accounting of how the funds are expended. Education is the priority. Social events or meals at CME activities cannot compete with or take precedence over the educational events. Independence must be preserved. A provider cannot be required by a commercial interest to accept advice or services concerning teachers, authors or participants, or other education matters including content from a commercial interest as conditions of contributing funds or services.

Standard 4—*appropriate management of associated commercial promotion*—guides the provider in keeping commercial promotion separate from continuing medical education. Product-promotion material or product-specific advertisement of any type is prohibited in or during CME activities. The juxtaposition of editorial and advertising material on the same products or subjects must be avoided. Whether live (staffed exhibits, presentations) or enduring (printed or electronic advertisements) promotional activities must be kept separate from CME. The standards provide specific strategies that keep advertising and education separated for print, computer-

based and live face-to-face CME activities. For *print CME*, advertisements and promotional materials cannot be interleaved within the pages of the CME content. For *computer-based CME*, advertisements and promotional materials cannot be visible on the screen at the same time as the CME content. For *live, face-to-face CME*, advertisements and promotional materials cannot be displayed or distributed in the educational space immediately before, during or after a CME activity. Providers cannot allow representatives of commercial interests to engage in sales or promotional activities while in the space or place of the CME activity. Arrangements for commercial exhibits or advertisements cannot influence planning or interfere with the presentation, nor can they be a condition of the provision of commercial support for CME activities.

Standard 5—content and format without commercial bias—directs providers to ensure that CME activities promote improvements or quality in health care and not a specific proprietary business interest or a commercial interest. Presentations must give a balanced view of therapeutic options. This is the essence of the difference between accredited CME and those events planned and presented by commercial interests. Use of generic names will contribute to this impartiality. If the CME educational material or content includes trade names, several companies' trade names should be used, where available—not just trade names from a single company.

Standard 6—disclosures relevant to potential commercial bias—invokes transparency as a strategy in continuing medical education. Prior to the beginning of the education activity learners must be provided with information about relevant financial relationships and the source of all support from commercial interests. Even when contributions are “in-kind,” the nature of the support must be disclosed to learners. For an individual teacher with no relevant financial relationships, the learners must be informed that no relevant financial relationships exist. This helps learners distinguish “missing information” from “no relevant relationships,” which ACCME believes is an important distinction to make.

New standards take effect soon

It is critical to ACCME that continuing medical education is presented in a context of independence from the commercial interests that fund a good part of the CME enterprise. In November 2006 ACCME begins making accreditation decisions based on these standards, adopted in 2004. Next, ACCME will focus on accreditation that promotes learning and change [7] in the context of practice-based change and improvement [8].

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 420-434.

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Virtual Mentor

Ethics Journal of the American Medical Association
June 2006, Volume 8, Number 6: 435-436.

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