

Marketing, Media, Wishful Thinking, and Conflicts of Interest: Inflating the Value of New Medical Technology

Richard A Deyo, MD, MPH

In 1991, Nelene Fox, a 38-year-old mother of three, was diagnosed with breast cancer. She underwent bilateral mastectomies and chemotherapy but nonetheless developed bony metastases. Her physicians said her only chance for survival was high-dose chemotherapy and autologous bone marrow transplantation. Her Health Maintenance Organization (HMO) refused to cover the procedure (around \$140,000) on the basis that it was experimental.¹

Her husband launched a successful fundraising effort, and Mrs Fox received the procedure, but died eight months later. Her brother, an attorney, sued the HMO for the delay in her therapy, and won \$89 million in damages. Similar lawsuits played out across the country with similar awards.

For the media, this was an irresistible David and Goliath story: relatively powerless individual patients were bringing insurance companies and HMOs to their knees. Reporting focused on access to the new technology, not questioning whether it was effective. With the media frenzy and lobbying, lawmakers began requiring insurance coverage for the new procedure. Insurers, facing lawsuits, bad publicity, and new legal requirements, began to routinely cover the new procedure.²

Physicians and hospitals were generally enthusiastic, optimistic,

and sincere in supporting the new regimen for late-stage breast cancer, and the new approach was a financial windfall for physicians and hospitals. Clinicians became vocal advocates for the procedure, and frequently were witnesses in court. Many joined complaints against insurers. Some hospitals built new wings to accommodate patients having the procedure.

However, as clinical trial results rolled in, the story began to unravel. An early positive report from researchers in South Africa proved to be fraudulent. National Institutes of Health (NIH)-sponsored trials, long delayed, finally showed the new treatment to be no more effective than standard chemotherapy, but more toxic. The trials were delayed because women were convinced the procedure was effective, and few were willing to submit to randomization with a chance of receiving standard therapy. By the time the negative results became available, 42,000 women in the US had been treated at a cost of \$3.4 billion.²

The approach was rapidly abandoned, but, in retrospect, medical theories, professional egos, wishful thinking, financial incentives, and the media helped disseminate a new technology that decreased quality of care and increased costs. Clinicians sincerely believed the treatment was effective, but theoretical advan-

tages and financial incentives may have obscured the lack of sound evidence. When access to care is a problem for millions of Americans, one may reasonably ask if there were better ways to deploy \$3.4 billion.

Other Technologies that Increased Cost, but not Quality

Other “advances” that increased costs without improving quality are easy to find. Rofecoxib (Vioxx) was recalled after its association with myocardial infarction became apparent, but only after, by one estimate, 140,000 avoidable heart attacks.³ Most who took it would have done as well with ibuprofen because they had a low risk of gastrointestinal bleeding.⁴ Nonetheless, rofecoxib resulted in expenditures of nearly \$2.5 billion per year while it was on the market.

Arthroscopic debridement and lavage for knee osteoarthritis has been a popular treatment. However, randomized trials suggest it is no more effective than sham surgery or rehabilitation.^{5,6} Nonetheless, costs of the procedure were estimated at \$3 billion per year.⁵

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) suggested that old-fashioned thiazides were at least as effective as several newer

Richard A Deyo, MD, MPH, is the Kaiser Permanente Professor of Evidence-Based Family Medicine, and Director of the OCTRI Community and Practice-Based Research Program at Oregon Health and Science University, in Portland, OR. E-mail: deyor@ohsu.edu.



drugs in preventing complications of hypertension.⁷ Nonetheless, their use had declined over several decades in favor of newer, more expensive drugs. Some estimated that greater use of diuretics might have prevented 70,000 myocardial infarctions and strokes per year⁸—and saved \$1.2 billion per year.⁹

These expensive, marginal treatments became widely used without adequate scientific evaluation or comparison to competing treatments. They demonstrate that new treatments are sometimes less effective or less safe than alternatives, yet we often learn this only after avoidable harm and expenditure.

These examples suggest that marketing, politics, media, and advocacy sometimes trump scientific considerations. Furthermore, physicians are often eager to adopt new technologies, hoping they will overcome the limitations of current approaches. However, “jumping the gun” before rigorous evaluation makes it hard for all of us to practice evidence-based medicine. And the resulting waste of resources occurs at a time when health costs are soaring and fewer Americans can afford insurance each year. Only recently have policy makers begun to address the need for better assessment of new technology and studies of comparative effectiveness.

Although many stakeholders share responsibility for disseminating marginal technology, an important factor has been the growth of industry-sponsored research,¹⁰ sometimes focused on getting the “right” results or masking the “wrong” results.¹¹ Sometimes professional organizations align with industry to suppress unwelcome results.¹² How do these events happen and how might we improve the trustworthiness of our scientific base?

Industry Sponsorship of Research: Getting the “Right” Results?

A growing literature documents that industry-sponsored research produces results favorable to its own products more often than independent research.¹³⁻¹⁸ For example, 90% of industry-sponsored trials of antipsychotic drugs favored the sponsor’s drug, sometimes producing contradictory results.¹⁹ Among trials comparing olanzapine with risperidone, those sponsored by Lilly favored olanzapine five times out of five. In contrast, trials sponsored by Janssen favored risperidone three times out of four.¹⁹

How can seemingly well-designed studies reach conflicting conclusions? There are several strategies for making research results as favorable as possible.

In designing a comparison group, one might choose a high dose of a competitor’s drug that produces more side-effects than the sponsor’s drug, or a less-effective low dose of the competing drug.^{19,20} In some studies, oral antifungals were compared to competitor drugs that were poorly absorbed by the oral route.²¹

Selective reporting of subgroups, side-effects, or outcome measures is another strategy. If just one subgroup shows an advantage for the sponsor’s drug, it may be reported without results for other groups. Similarly, if one outcome measure among several shows a favorable result, it may be reported to the exclusion of others.²⁰

Another strategy is to publish favorable results multiple times. Authors of a systematic review on risperidone found the literature to be “vexing,” “bewildering,” and “intolerably time consuming” because of overlapping reports.²² They discovered that 20 articles

and several unpublished reports actually represented only seven small studies and two large ones. One larger study was reported in six publications with different authors and no reference to the others. Similar redundant reports have been identified for ondansetron, fluconazole, and nonsteroidal anti-inflammatory drugs. In each case, the duplicate data inflate apparent drug efficacy.²²⁻²³

Ghost writing and guest authorship comprise another important strategy for favorable publications. In this situation, research reports, editorials, or reviews are written by a professional writer hired by a drug company or a public relations firm. A medical authority is invited to be named as the author, and gives final approval to the article. The ghost writer’s name does not appear, but s/he has already framed the arguments in the most favorable light. In “Whose article is it anyway?” by Marilynne Larkin, writer Ronni Sandroff described her experience in writing two cancer pain articles “for MD signatures” intended for peer-review journals. She was told exactly what the drug company expected and given explicit instructions about what to play up and what to play down.²⁴ Recent revelations regarding rofecoxib demonstrate that dozens of articles were prepared in this way.²⁵

Suppressing Unfavorable Results

Finally, unfavorable trial results can be buried. Companies argue that their data are proprietary and there is no requirement that all results be published. A recent examination of FDA-registered studies for antidepressant drugs illustrated the problem. Of 74 registered studies, only 51% had a positive result for the sponsor’s drug according to FDA

review. However, 94% of published trials favored the sponsors' drugs. Among 36 studies that the FDA judged as negative or questionable, 22 were never published; 11 were published with a positive spin to the discussion; and only three were published as negative trials.²⁶

Company-sponsored research conducted by university investigators may seem less susceptible to manipulation. However, a recent survey of university-industry agreements suggested that academic institutions routinely participate in clinical research that does not adhere to recommended standards (from medical editors) for accountability, access to data, and control over publication.²⁷

A striking example of suppressing results occurred at the University of California, San Francisco. In 1987, Betty Dong, MD, was approached by the predecessor to Boots pharmaceuticals, maker of Synthroid (generic: levothyroxine), to compare its product with generic competitors. Synthroid had dominated the market, thanks to concerns that other thyroid preparations had less consistent bioavailability. However, Synthroid's market share was eroding, so Dr Dong was approached to compare Synthroid with three competitor drugs.²⁸

Dr Dong's study, completed in 1990, unexpectedly found that the four preparations of thyroid hormone were equivalent. Although Boots had handpicked Dr Dong, specified the study design, and made frequent quality assurance visits, executives suddenly objected to nearly all aspects of the study, and complained to university officials. Two investigations found only minor and easily correctible problems. One outside expert said, "The Boots people were deceptive and self-serving."²⁹

These events were a prelude to legal threats that blocked publication of the results. The company cited a clause in Dr Dong's contract, even though restrictions on publication were contrary to university policy. This occurred in 1994, when Dong's paper was accepted at the *Journal of the American Medical Association (JAMA)*. Two weeks before scheduled publication, in the face of legal threats, the authors withdrew the manuscript.

While these events were unfolding, Boots was selling its drug division to a German company for \$1.4 billion. Boots became part of Knoll Pharmaceuticals, and analysts suggested that publication of Dr Dong's results would have been disastrous for Boots and its sale value.²⁹

Eventually, in the face of negative publicity and pressure from the Food and Drug Administration for possibly misleading claims, the company relented. In April 1997, *JAMA* published the article along with Knoll's cautious apology and continued objections.^{28,30}

Knoll subsequently faced a class action lawsuit by consumers, alleging they were overcharged for medication because data on bioequivalence were unavailable. Knoll denied efforts to suppress publication but offered \$135 million to settle the suit. Knoll later paid 37 states another \$41.8 million to settle charges that it made deceptive statements about Synthroid.

Although this episode may seem extraordinary, attempts to suppress unwelcome news may be business as usual. Herb Needleman, MD, of Yale was attacked by the lead paint industry for many years, after demonstrating the neurotoxicity of lead in children. In 2007, the makers of OxyContin, the brand name for the time-released oxycodone, pled guilty to fraudulent marketing

claims and agreed to \$634 million in fines, after hiding data on addictive properties of the drug.³¹ Similar claims of suppressing bad news and intimidating investigators appear with alarming frequency.

Attacks on Funding Agencies

Another strategy for minimizing bad news is to attack research agencies that fund unwelcome research. Examples included efforts to eliminate the Injury Prevention Branch at the Centers for Disease Control after it funded studies demonstrating a higher risk of gun violence in the homes of gun owners. Attacks came from the National Rifle Association and a group called "Doctors for Integrity in Research and Public Policy," with views similar to those of the NRA.³² The National Center for Health Care Technology was a government agency with a brief lifespan in the 1970s, eliminated after lobbying by the drug and medical device industries.³³ The Agency for Health Care Policy and Research (AHCPR) was almost eliminated after lobbying by a physician organization upset with research and guidelines the agency sponsored.¹²

In this last example, our research team demonstrated in the 1990s that spinal fusion surgery was the fastest growing type of back surgery in the US. At the time, pedicle screws were a relatively new technology for this type of surgery, and were growing in popularity. Our work challenged the effectiveness and safety of fusion surgery for some common indications, and recommended that it be subjected to randomized controlled trials.

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At the same time, a multidisciplinary panel sponsored by the same agency was producing clinical guidelines for acute low back pain. On the basis of extensive evidence, the panel recommended nonsurgical therapy for most acute back problems, noting there were no trials of fusion surgery for patients with acute back pain.

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These findings elicited a backlash from the North American Spine Society, a multidisciplinary group dominated by orthopedic surgeons. The Society organized a letter-writing campaign to Congress, arguing for elimination of the AHCPR. A member of the Society's board founded an advocacy organization dedicated to this aim. Finally, a manufacturer of pedicle screws sought a court injunction to block release of the back pain guidelines.¹²

These events unfolded during Congressional controversy over the Clinton health plan and leadership of the AHCPR. The combination resulted in a House bill in 1996 that eliminated the AHCPR. The agency was restored by the Senate after strong support from other professional societies, including the American Medical Association and the American College of Physicians. Nonetheless, the AHCPR ended its guideline work altogether and sustained a 25% budget cut, eliminating new research for several years and reducing existing grant budgets.

The story continues today. Several spinal device manufacturers are currently under investigation for alleged kickbacks to surgeons. In 2006, one company paid \$40 million to the US government to settle accusations of "sham consulting

agreements, sham royalty agreements, and lavish trips," without acknowledging any wrongdoing.³⁴

Consequences of Inadequate Research and Suppressing Data

Several important consequences may arise from suppressing research results, influencing scientific reports, or inadequately evaluating medical innovations. First, patients may be exposed to unnecessary risks. Second, harassment discourages research in controversial areas, exactly those most needing good scientific study. In effect, vested interests may determine the acceptable research questions and results. Eliminating public peer-reviewed scientific research funding may slow the emergence of new knowledge and push investigators to seek funding associated with conflicts of interests.¹² Ultimately, disseminating marginal or ineffective technology increases costs of care without increasing quality, complicating health care reform.

Improving the Evaluation and Value of New Technology

What are some potential solutions to these problems? First, for physicians, a renewed sense of professionalism may be essential. While we value the professional attributes of altruism, service, self-governance, and deep knowledge, the business ethos is quite different. Here, the primary responsibility is not to patients but to shareholders. The drug, device, and supply industries create many jobs, and the main focus of attention is return on investment. This contrast between professional and business priorities led the Association of American Medical Colleges to argue recently that doctors, staff, and students in

medical schools should avoid certain entanglements with industry. It recommended that individuals not accept free food, gifts, or travel from drug and device companies and not accept ghost-writing services. The report strongly discouraged participation in company-sponsored speakers bureaus.³⁵

Practicing physicians should become familiar with the rules of evidence-based medicine, as a safeguard against misleading claims. A simple-minded definition of evidence-based medicine would argue that it is not enough to know if a treatment ought to work; if it makes physiologic sense; if it is common practice; if we learned it in medical school; if we've always done it that way; if an expert vouches for it; or if it works in mice.³⁶ Instead, we need to ask what is the best evidence that a new treatment extends lives or improves quality of life, and what are the risks?

In addition, regulatory reforms are needed. Direct comparisons of competing drugs and devices are rarely mandated by the FDA but would be enormously valuable to physicians and patients. Legislative proposals for studying comparative effectiveness deserve support. Most agree that the FDA needs more resources and better methods for post-marketing surveillance of drug and device safety. I favor a requirement for randomized trials for devices that are surgically implanted in the body. The current threshold for approval is far less rigorous than for drugs, yet the need for evidence of clinical efficacy and safety is equally great. Both private and government insurers could help produce better evidence by supporting clinical trials as a condition of coverage when the evidence for new technology is weak.³⁷

For the research enterprise, the peer review system must resist

external influences in grant review and publication. This requires eliminating efforts to block publication, reviewers with conflicts of interests, and threats to editors from their advertisers. In some cases, new university policies may be necessary to support faculty who come under attack from vested interests. Public funding agencies should be vigorously defended.

For investigators themselves, it is essential to strive for impeccable science, and to have thick skin. Research on product effectiveness is a contact sport, and investigators should anticipate a backlash, including character attacks and intimidation, to unfavorable results.

Finally, we should foster more realistic public expectations of new medical technology. Americans, more than Canadians or Europeans, believe new technology can solve all our serious medical problems.³⁸ We sometimes foster such expectations with our own wishful thinking, and because it is financially convenient to generate more procedures and more care. However, the public must understand now more than ever that “newly approved” does not necessarily mean new and improved.³⁹ This understanding may be critical to freeing resources that facilitate better access to care. ❖

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That Which Shrinks

It is error only, and not truth, that shrinks from inquiry.

— Thomas Paine, 1737-1809, philosopher and writer