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How big drug companies
compromise doctors,
undermine the top journals,
and slow medical research

Medicine for Sale

HAROLD A. WASSERMAN

Also
Winston Churchill
Flea Circuses
The Mexican
Border
New Fiction,
New Poetry

COVER STORY

Flacking for Big Pharma

DRUGMAKERS DON'T JUST COMPROMISE DOCTORS;
THEY ALSO UNDERMINE THE TOP MEDICAL JOURNALS
AND SKEW THE FINDINGS OF MEDICAL RESEARCH

HARRIET A. WASHINGTON

“DRUG MAKERS Cut Out Goodies for Doctors” and “Drugmakers Pulling Plug on Free Pens, Mugs & Pads” read headlines in *The New York Times* and *The Wall Street Journal* Health Blog at the end of 2008 after, in a very public act of contrition, 38 members of the pharmaceutical industry vowed to cease bestowing on prescribing physicians goodies such as pens, mugs, and other tchotchkes branded with their names. Some physicians and ethicists had long expressed concern about the “relationship of reciprocity” that even a pizza or cheap mug can establish between doctors and drugmakers, and branded trinkets also send a message to the patient, who might reason that Gardasil must be a good drug if her doctor wields a reflex hammer inscribed with its name. But while the popular press celebrated this sudden attack of nanoconscience and while we still gravely debate whether physicians’ loyalties can really be bought

for a disposable pen or a free lunch, the \$310 billion pharmaceutical industry quietly buys something far more influential: the contents of medical journals and, all too often, the trajectory of medical research itself.

How can this be? Flimsy plastic pens that scream the virtues of Vioxx and articles published in the pages of *The New England Journal of Medicine* would seem to mark the two poles of medical influence. Scarcely any doctor admits to being influenced by the former; every doctor boasts of being guided by the latter. In fact, medical-journal articles are widely embraced as irreproachable bastions of disinterested scientific evaluation

Harriet A. Washington is the author of *Medical Apartheid: The Dark History of Medical Experimentation on Black Americans from Colonial Times to the Present*, which won the 2007 National Book Critics Circle Award for Nonfiction. Her new book, *Deadly Monopolies: The Shocking Corporate Takeover of Life Itself—And the Consequences for Our Health and Our Medical Future*, will be published in October.

and as antidotes to the long fiscal arm of pharmaceutical-industry influence.

And yet, “All journals are bought—or at least cleverly used—by the pharmaceutical industry,” says Richard Smith, former editor of the *British Medical Journal*, who now sits on the board of Public Library of Science (PLOS), a nonprofit open-access group publishing scientific journals that eschew corporate financing and are freely available online to the public.

Big Pharma, as the top tier of the industry is known, starts modestly, inserting the thin edge of its wedge by advertising copiously—and often inaccurately—in medical journals. In 1981, concerned officials at the Food and Drug Administration recognized the educational nature of pharmaceutical advertising by establishing explicit standards for medical-journal ads that mandate “true statements relating to side effects, contraindications, and effectiveness,” and a “fair balance” of statements about medication risks and benefits.

In 1992, the editors of the esteemed *Annals of Internal Medicine* decided to gauge how well their own advertisements met that standard. They tested 109 advertisements along with the references cited by those ads, sending each ad to three expert reviewers who evaluated them in light of the FDA standards. Fifty-seven percent of the ads were judged to have no educational value, 40 percent failed the fair-balance test, and 44 percent, the reviewers believed, would result in improper prescribing. Overall, reviewers would have recommended against publication of 28 percent of the advertisements, as the *Annals* revealed in its published report.

The FDA subsequently issued 88 letters accusing drug companies of advertising violations between August 1997 and August 2002. But the *Annals* editors were in no position to bask in this validation: the journal was fighting for its life after large pharmaceutical companies withdrew \$1.5 million in advertising. “Finally, the editors felt that to save the journal, they must resign,” recalls Smith. The coeditor of the *Annals*, Robert Fletcher, remarked as he departed his job: “The pharmaceutical industry showed us that the advertising dollar could be a two-edged sword, a carrot or a stick. If you ever wondered whether they play hardball, that was a pretty good demonstration that they do.”

A decade later, with a different editor at the helm and a restored pharmaceutical advertising base, the *Annals* planned an editorial on high drug prices. But this time, it took care to first invite commentary from the premier drugmakers’ organization, the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA in turn funded a piece by John E. Calfee of the American Enterprise Institute, whose essay began with the statement “Price controls could have a substantial negative effect on pharmaceutical research and development.”

Pharmaceutical advertising impinges heavily on the editorial sphere of medical journals, sometimes with surprising brazenness. The drug epoetin is widely accepted for its role in prolonging survival in people with end-stage renal disease: Medicare alone

spent \$7.5 billion on the drug in the decade preceding 2002. Dennis Cotter is president of a nonprofit institute that scrutinizes conventional medical wisdom, and his group's analysis suggested that epoetin's benefits for people with end-stage renal disease were largely chimerical, based on flawed logic. In 2003, Cotter submitted an editorial that detailed his questioning of epoetin's role to *Transplantation and Dialysis*, whose editor and peer reviewers agreed that it should be published. However, as the *British Medical Journal* reported in January 2004, Joseph Herman, *Transplantation and Dialysis's* editor, rejected the piece because "unfortunately, I have been overruled by our marketing department with regard to publishing your editorial. The publication of your editorial would, in fact, not be accepted in some quarters . . . and apparently went beyond what our marketing department was willing to accommodate."

After a hue and cry was raised in the medical press, the journal reversed itself and offered to publish Cotter's work, but he demurred, preferring a less commercial venue.

Medical journals are utterly dependent upon pharmaceutical advertising, which can provide between 97 and 99 percent of their advertising revenue. By 2005, some major journals, including *Consultant*, *Geriatrics*, and *American Family Physician*, carried more advertising than editorial pages and glossy, full-color inserts that were longer than the journal's longest article. This explains why medical journals themselves advertise to drugmakers, flooding the pages of pharmaceutical-industry publications such as *Medical Marketing and Media* to vie for the attentions of Big Pharma. The *Journal of the American Medical Association (JAMA)* bills itself in advertising as "a priceless audience at a price you can afford," while the *Annals* boasts: "With an audience of more than 90,000 internists (93 percent of whom are actively practicing physicians), *Annals* has always been a smart buy."

Moreover, drugmakers sometimes agree to buy journal advertising only if it is accompanied by favorable editorial mentions of their products. Or their in-house stables of writers or hired pens generate "advertorials," a Frankensteinian mix of medical content and marketing messages that can be indistinguishable from editorial material. "Pharmaceutical firms also inform journals," Smith observes, "that they are receptive to buying huge volumes of reprints that favor their wares: The profits for the journal can easily reach \$100,000."

Pharma's journal ads tout not only products but also its hundreds of thousands of subsidized "educational opportunities." Drug and medical-device makers spend \$2 billion annually for more than 300,000 seminars and training opportunities, often held in the Bahamas or the Caribbean. The wolfed-on-the-run free pizza for harried medical residents that the industry has so sanctimoniously forsworn bears little resemblance to the sumptuous feasts, flowing wines, chartered flights, cruises, luxurious lodgings, golfing, snorkeling, and remarkably attractive sales reps that characterize these island educational junkets.

"There's a lot of bribery involved—the kids get pizza, the grownups get trips to

Hawaii,” observed Marcia Angell, MD, professor of social medicine at the Harvard Medical School, former editor-in-chief of the *New England Journal of Medicine (NEJM)*, and the author in 2004 of *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*.

These pedagogic playdates familiarize doctors with pharmaceutical companies’ patented products to the exclusion of cheaper and sometimes safer and more effective alternatives. By 2000, drugmakers were paying physicians a total of \$6 billion a year for trinkets, island “educational opportunities,” and financial grants for their pet projects, from golfing jaunts to clinics; this doesn’t include the speaking and consulting fees that the pharmaceutical industry pays influential and “high-prescribing” clinicians to discuss its products. “Drug companies have moved their gift-giving from drug reps to hiring ‘thought leaders’—the best drug reps of all,” says Angell. “They send experienced physicians out to give talks and ensconce them on well-paid speakers’ bureaus. Then they claim that this is education, not marketing.”

However, the industry’s seduction doesn’t end with the advertisements, junkets, and overpaid speaking engagements. Drugmakers have enticed or ensnared the very font of evidence-based medical knowledge—the peer-reviewed medical journal. Not content to turn these journals out to ply the streets for cash, the industry finds many ways to pervert the editorial content itself.



“There’s a lot of bribery involved,” according to Marcia Angell, MD, of Harvard Medical School. “The kids get pizza, the grownups get trips to Hawaii.”

THIS PERVERSION is such an open secret that in 2003 the *British Medical Journal* published a tongue-in-cheek essay instructing researchers in the fine art of “HARLOT—How to Achieve positive Results without actually Lying to Overcome the Truth.” David L. Sackett, director of Ontario’s Trout Research and Education Center, and Andrew D. Oxman, director of the Department of Health Services Research at Norway’s Directorate for Health and Social Welfare, wittily summarized strategies by which drugmakers use clinical trials to tart up drugs that are poorly performing, dangerous, or both.

The proper conduct of a research study requires that it pose an important medical question in a clear, unambiguous manner and that it is carefully planned and randomized to ensure that the results are accurate and broadly applicable. Large numbers of subjects are typically recruited to help ensure that the results do not arise by chance. Control groups are given placebos or the standard of care in order to allow a meaningful comparison with the study group. Statistical expert-

ise helps the study designers minimize and tease out any sources of error or bias.

But this expertise can also be used to introduce intentional bias in order to attain the desired result: for the determined adept, there exist many ways to subvert the clinical-trial process for marketing purposes, and the pharmaceutical industry seems to have found them all.

HARLOT's advice to those who would serve Pharma includes, "test against placebo, test against minimal dose, test against maximal dose, and test in very small groups." This means that companies sometimes seek to make bad drugs look good by:

- *Comparing their drug to a placebo.* A placebo, such as a sham or "sugar" pill, has no active ingredient, and, although placebos may evoke some poorly understood medical benefits, called the "placebo effect," they are weak: medications tend to outperform placebos. Placebo studies are not ethical when a treatment already exists for a disorder, because it means that some in the study go untreated. However, if you care only that your new drug shines in print, testing against placebo is the way to go.

- *Comparing their drug to a competitor's medication in the wrong strength.* Too low a dose makes the rival drug look ineffective. Too high a dose tends to elicit worrisome side effects.

- *Pairing their drug with one that is known to work well.* This can hide the fact that a tested medication is weak or ineffective.

- *Truncating a trial.* Drugmakers sometimes end a clinical trial when they have reason to believe that it is about to reveal widespread side effects or a lack of effectiveness—or when they see other clues that the trial is going south.

- *Testing in very small groups.* Drug-funded researchers also conduct trials that are too small to show differences between competitor drugs. Or they use multiple endpoints, then selectively publish only those that give favorable results, or they "cherry-pick" positive-sounding results from multicenter trials.

An increasingly popular variant is the much-abused technique of "data mining," wherein small subgroups of an unsuccessful trial are relentlessly scrutinized in search of groups for whom a benefit emerges, or seems to.

When he sought a novel way to focus attention on the frequently deceptive nature of data mining, Dr. Peter Sleight, professor of cardiovascular medicine at Oxford University, might have been guided by Molière's advice: "One easily bears moral reproof, but never mockery." Accordingly, in lieu of ethical finger wagging, Sleight illuminated the dangers of data mining by using mockery, stratifying some drugs' effectiveness by astrological sign. In 1988, he and his team analyzed the data of the International Study of Infarct Survival (ISIS-2), a real, 17,000-person clinical trial in the United Kingdom that asked whether aspirin helped people who had suffered a recent heart attack. This study found that the beneficial effect of aspirin for patients having a heart attack was quite as powerful as that of streptokinase, another effective clot-dissolving medication.

But when Sleight sorted the patients' responses by astrological subgroup, taking aspirin was associated with a good outcome for all birth signs except for Libra and Gemini, who were more likely to die when given aspirin. In 1985, another large study, ISIS-1, had found a 71 percent reduction in the death rate of people born between July 24 and August 23 (Leos), who took the beta-blocker atenolol, as compared to people of all other birth signs, who enjoyed a mortality reduction of only 24 percent. Sleight concluded with this warning: "When in a trial with a clearly positive overall result, many subgroup analyses are considered, false negative results in some particular subgroups must be expected."

In 2005, BiDil, a congestive heart-failure medication, became the first FDA-approved drug for African Americans only. BiDil was not tailored for African Americans, as its proponents often claim, but began life as the only patented drug of the Lexington, Massachusetts, biotech firm NitroMed. In 1987, the FDA had rejected NitroMed's application based on feeble results in its clinical trials, but the company scrutinized the drug's data in search of some group where it might show efficacy. Peering into BiDil's efficacy in women and in other subgroups yielded no fruit, but before NitroMed had to resort to astrology, the NIH passed the FDA Modernization Act, an initiative for the inclusion of racial minorities in clinical trials. NitroMed suddenly detected evidence in the FDA-rejected 1980s data that its drug might work better for blacks than it had for whites, and in 1997 BiDil was reborn as a "black" drug.



Studies published in the best medical journals get "a certain imprimatur that makes people less critical," says Dr. Joel Lexchin, a bioethicist at York University.

BiDil proponents published studies that supported their claim of a racially mediated genetic anomaly that was addressed by BiDil, making it an ideal drug for blacks but not for whites. At the company's invitation, other physicians published papers arguing for this genetic racial difference, but they could do so only by giving short shrift to critically important environmental and behavioral differences between black and white patients, such as disparate diets, smoking rates, environmental exposures, and exercise levels. NitroMed won FDA approval of a new trial that included only 1,050 black subjects, with no white subjects to provide comparison data. Furthermore, BiDil was not tested alone, but only in concert with heart medications that are already known to work, such as diuretics, beta-blockers, and angiotensin-converting enzyme (or ACE) inhibitors. The published results of the trial were heralded as a success when subjects taking the drug combinations that included BiDil enjoyed 43 percent fewer heart-failure deaths.

The zealous data mining and the pairing of BiDil with drugs that are known to work well are recognizable tenets of HARLOT. Moreover, excluding whites was a medically illogical but

financially strategic move because it eliminated the possibility that the drug would test well in whites, thereby robbing NitroMed of its already thin rationale for calling BiDil a black drug. The “black” label was crucial, because BiDil’s patent covering use in all ethnic groups expired in 2007, but the patent for blacks only allows NitroMed to profit from it until 2020. BiDil is a case study in research methodology “flaws” that mask strategies calculated to make a dodgy drug look good on paper, for profit.

THE MEDICAL RECORD is also effectively distorted through what is *not* said, suggests Marcia Angell. “Any reputable journal is at the mercy of what is submitted to it,” she says, “and must choose from whatever comes over the transom. Many studies never see the light of day because their findings are negative. There is a heavy bias toward positive studies, and this negative bias is a real problem. A company may conduct 1,000 trials; if two are positive, they get FDA approval and are published. The other 998 never see the light of day.” In fact, half of all study data is never published.

But aren’t physicians, with their scientific training and medical expertise, able to see through the negative bias and data manipulation? Not according to the editor of the *Journal of the National Medical Association*. “A busy pediatrician who is seeing patients until eight at night doesn’t have time to figure out whether an article has been vetted,” explains Eddie L. Hoover, MD. “He depends upon the journal editors to make sure he is not reading trash.”

“When you are published in a medical journal, especially one of the top ones, this gives the article a certain imprimatur that makes people less critical,” adds Joel Lexchin, MD, a bioethicist at York University in Toronto. “If it’s in *The New England Journal of Medicine* it’s got to be good’: This mentality diminishes the critical reading of the study.” Moreover, many inaccuracies cannot be detected because neither the journal nor the reader has access to all of the original trial data. In the end, explains Angell, “Journals get a heavily winnowed-out selection of trial findings, and so doctors come to believe that medications in trials are more effective than they are. Many psychiatric medications are little more than placebos, yet many clinicians have come to believe that SSRI [selective serotonin reuptake inhibitors, a newer class of antidepressants] drugs are magic, all through the suppression of negative studies.”

Howard Bauchner, MD, the recently named editor of *JAMA*, points out that “one of the best advances, undertaken under [former *JAMA* editor] Catherine DeAngelis, MD, is the requirement to register for clinical trials: This provides an important opportunity for journals as the final conduits for research in the U.S. to understand and ensure that what is being reported represents the intent of the investigators, an important safeguard.” Bauchner is speaking of a 2004 innovation, when a group of a dozen editors of esteemed medical journals jointly announced that they would publish no drug-research study sponsored by a pharmaceutical company unless it

was registered from its outset in a public database.

Mandatory registration of research with drugs, biologics, and devices on ClinicalTrials.gov was duly established as part of the FDA Modernization Act of 1997 and was intended to counteract negative bias by preventing the widespread suppression and selective reporting of results. The 100,000 trials on the site inform readers of the existence of unpublished studies that may find medications to be wholly or partially ineffective or dangerous. However, its director, Deborah Zarin, MD, warns: “Some invalid data can be detected by ClinicalTrials.gov staff; however, other data cannot be verified because ClinicalTrials.gov does not have an independent source of study data.” In other words, the database must rely on investigators and their corporate sponsors to submit complete and accurate data.

Incredible as it sounds, the pharmaceutical code of silence extends to refusing to publish troubling data or even to release it to the researchers that collected it. In the *United States of America vs. Forest Laboratories*, the government charged that Forest concealed damning data from its own medical researchers, from other medical personnel, and from sales staff. These data revealed that the drug Lexapro (escitalopram) for depression and anxiety disorders was relatively ineffective when taken by children. However, U.S. prosecutors averred that from 2001 to 2004, Forest widely publicized only data from a single study it financed, which showed that Lexapro worked.

Silence also reigns on side effects, notes Angell. “When we would spot bias and turn down a paper at the *NEJM*, we’d call the author to point out, ‘You didn’t mention side effects.’ He would say ‘The sponsor wouldn’t let us do that.’ Later, the paper would turn up unchanged elsewhere, in another journal.”

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WHEN JOHN ABRAMSON, MD, author of *Overdosed America: The Broken Promise of American Medicine*, lectured at Harvard’s 2008 Ethical Issues in Global Health Research course, he dismissed much of the content of contemporary U.S. medical journals as “little better than infomercials.” What prompted this harsh assessment?

Despite the ubiquitous mantra of “evidence-based medicine,” a curious lack of skepticism pervades journals about experts who accept money from the makers of the products they evaluate. A medical reviewer who writes a comprehensive assessment for a medical journal is supposed to be an expert in the field who evaluates medications, devices, and practices, distilling her expertise and her informed, disinterested opinion for the journal’s readership. The need for objectivity is clear, and journals do



Much of the content of contemporary U.S. medical journals is “little better than infomercials,” according to John Abramson, MD, the author of *Overdosed America*.

not pay the authors of such articles. But the makers of the drugs and products in question often do pay them.

Once, conscientious journals did not permit reviewers to take money from drugmakers. But so many physicians began to take Pharma money to subsidize their research, to give speeches on behalf of favored new products, and to switch their patients to newer, more profitable medications, that working as a medical reviewer in the pay of drugmakers has become normalized. Today, medical-journal editors estimate that 95 percent of the academic-medicine specialists who assess patented treatments have financial relationships with pharmaceutical companies, and even the prestigious *NEJM* gave up its search for objective reviewers in June 1992, announcing that it could find no reviewers that did not accept industry funds.

Instead, financial disclosure has been pressed into service as a substitute for objectivity. These notices inform the reader which company paid the author, but neither how much nor what nonmonetary relationship the author may be enjoying with the subject of his assessment. Medical journals usually set a ceiling on the payments that evaluating doctors are permitted to accept from drugmakers, but these ceilings are high and vaulted, with the top-tier journals tending to publish the work of the reviewers who receive the fattest Pharma paychecks. Under the *NEJM* policy, for example, doctors writing medical reviews can accept up to \$10,000 a year in speaking fees and consulting fees from each drug company. "So if a doctor is doing . . . business with four or five companies, he or she can get as much as \$40,000 to \$50,000 a year and not violate the *New England Journal* policy," says Dr. Sidney Wolfe, director of Public Citizen's Health Research Group.

When physician-researchers are paid by the pharmaceutical industry, their medical-journal findings exhibit clear bias in line with the interests of the sponsoring company. Drs. Paul M. Ridker and Jose Torres at Harvard Medical School found that 67 percent of the results of industry-sponsored trials published between 2000 and 2005 in the three most influential medical publications favored the sponsoring company's experimental heart drugs and often its devices. Trials funded by nonprofits, however, were as likely to support the drugs or devices as to oppose them, and studies that combined industry funding with nonprofit support fell between the two on the spectrum, with 57 percent offering favorable results. The findings, published in *JAMA*, indicate that large pharmaceutical and device makers pay for studies on new medical treatments in hopes of replacing the current standard of care with their new therapy.

Not all clinical trials are performed to evaluate treatments: some are marketing tools. Drugmakers conduct *seeding trials* that induce many physicians to prescribe the drug, and then its effects are reported selectively, so that many articles extol the drug's positive results while any troubling findings are ignored. In *switching trials* physicians are induced by drug reps to switch their patients from an older medication to a newer one, and again, positive results are selectively published. The posi-

tive data from such trials are submitted for publication by different investigators in different guises so that journal editors have no way of knowing whether they are publishing new data or a retread.

“I’m very concerned about journals reprinting the same material from the same studies over and over,” says Hoover, the *Journal of the National Medical Association* editor. “How do you ensure that the information you are publishing is unique?” Editors usually cannot, says Abramson, the *Overdosed America* author, who has served as an expert witness in cases involving allegations of misrepresentation by pharmaceutical companies. “Without a subpoena, you can’t know what really happened. With one, there is access to original documents that paint a stunningly different picture of data manipulation; unfortunately these documents usually remain sealed after litigation.”

Fortunately, some documents do escape Pharma’s sealed files. Lawsuits against pharmaceutical companies have resulted in rulings that forced the publication of the Drug Industry Document Archive, a searchable database (<http://dida.library.ucsf.edu>) of thousands of pages of industry documents on the Internet, just as major tobacco companies were forced to do as a condition of successful lawsuits against them in the 1990s.

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MANY BIASED MEDICAL-JOURNAL ARTICLES are the work not of physicians or scientists, but of ghostwriters who script them in accordance with the drugmakers’ marketing messages. A medical expert is found who, for a few thousand dollars, is willing to append his or her signature, and then the piece is published without any disclosure of the ghostwriter’s role.

Adriane Fugh-Berman, MD, is the director of PharmedOut, at Georgetown University Medical Center. PharmedOut is a medical education and analysis center that traces the effect of corporate funds on medicine. It was created as part of a 2004 settlement between Warner-Lambert and U.S. Attorneys General over allegations that the company conducted an unlawful marketing campaign for one of its drugs. In September 2010, Fugh-Berman drew back the veil on a ghostwriting campaign in which Wyeth (a drugmaker now a part of Pfizer) paid the publicity firm DesignWrite to generate journal reviews that helped promote Premarin and Prempro, its brands of hormone replacement therapy (HRT), to prescribing physicians. By shoring up hormone levels, HRT promised to preserve health and femininity indefinitely by treating the biological torments triggered by menopause, such as heart disorders, troubled skin, hot flashes, vaginal dryness, and insomnia.

But some medical data suggested links between HRT and cancer, so an alarmed Wyeth poured resources into addressing this hazard, but not by seeking to counteract the risks or by warning physicians. Instead, Wyeth hired DesignWrite’s stable of ghostwriters, who promulgated the company’s sales messages in the form of more than 50 articles for peer-reviewed medical journals, as well as supplements, medical



Dr. Adriane Fugh-Berman of Georgetown Medical Center, in an article on ghostwriting in medical journals, showed how marketing messages can trump the research data.

abstracts, and reports. Between 1997 and 2003, DesignWrite scribes followed Wyeth's instructions to, as Fugh-Berman notes in her article, "mitigate perceived risks of hormone-associated breast cancer," to "promote unproven, off-label uses, including prevention of dementia, Parkinson's disease, and visual impairment," to "raise questions about the safety and efficacy of competing therapies (competitive messaging)," to "defend cardiovascular benefits," and to "position low-dose hormone therapy."

Some argue that ghostwriting is not problematic because it is based on research data. But Fugh-Berman's article "The Haunting of Medical Journals: How Ghostwriting Sold 'HRT'" from *PLoS Medicine* explained that when research data conflicted with the marketing message, the former had to give way, as when DesignWrite emailed James H. Pickar, MD, to explain the absence of a Premarin/trimegestone combination that was deleted from a Wyeth report in 2003. The memo noted: "It is highly desirable for them [the marketing team] to not have the metabolic data included in the lead paper, as this would cause labeling problems, making the lead paper unusable for promotional purposes." Fugh-Berman also revealed that Wyeth ped-

dled pieces that denied HRT's cardiovascular risks with claims that were not supported by the medical evidence; and its writers falsely claimed that the breast cancers associated with HRT were less aggressive than other breast cancers.

Wyeth kept its ghostwriters busy on the editorial track, and 18 medical journals published DesignWrite's HRT spin control, including the venerable *American Journal of Obstetrics and Gynecology* and the *International Journal of Cardiology*. Between the introduction of Prempro in 1995 and 2002, 13 million women, representing 38 percent of the postmenopausal women in the United States, were taking HRT, garnering \$3 billion in sales a year.

But in 2002, the *Journal of the American Medical Association* flipped the HRT script when it published the unspun results of a Women's Health Initiative study of 16,000 U.S. women on HRT. The drugs in Premarin and Prempro elevated the risk of the diseases they were intended to prevent, resulting in a 41 percent increase in stroke risk, a 29 percent increase in heart attack risk, a 26 percent increase in the risk of breast cancer, and a 22 percent increase in cardiovascular disease risks. These revelations about the dangers of HRT prompted many doctors to withdraw most of their patients from its drug regimens. However, Wyeth persisted in "educational" efforts, such as seminars directed at defecting doctors—some scripted by the ghostwriters of DesignWrite.

Ghostwriting has been used to promote many drugs, including the antidepressant

Paxil (paroxetine); the recalled weight-loss drug “Fen-Phen” (fenfluramine and phentermine); the anti-epilepsy drug Neurontin (gabapentin); the antidepressant Zoloft (sertraline); as well as the painkiller Vioxx (rofecoxib)—to name just a few.

In 2003, the medical-publishing industry seems to have hit a ghostwriting nadir from which its reputation has not recovered. That year, Elsevier, the Dutch publisher of both *The Lancet* and *Gray’s Anatomy*, sullied its pristine reputation by publishing an entire sham medical journal devoted solely to promoting Merck products. Elsevier publishes 2,000 scientific journals and 20,000 book-length works, but its *Australasian Journal of Bone and Joint Medicine*, which looks just like a medical journal, and was described as such, was not a peer-reviewed medical journal but rather a collection of reprinted articles that Merck paid Elsevier to publish. At least some of the articles were ghostwritten, and all lavished unalloyed praise on Merck drugs, such as its troubled painkiller Vioxx. There was no disclosure of Merck’s sponsorship. Librarian and analyst Jonathan Rochkind found five similar mock journals, also paid for by Merck and touted as genuine. The ersatz journals are still being printed and circulated, according to Rochkind, and 50 more Elsevier journals appear to be Big Pharma advertisements passed off as medical publications. Rochkind’s forensic librarianship has exposed the all-but-inaccessible queen of medical publishing as a high-priced call girl.

NOT CONTENT to skew reports of clinical trials on the back end, pharmaceutical companies also manipulate medical studies to generate the desired data for those reports. Studies are constructed in a manner that presents drugmakers’ products in the most positive light or throws doubts on the seemingly clear hazards of taking their drugs.

Around 1999, pharmaceutical firms instructed their sales representatives to heavily promote expensive new COX-2 inhibitors such as Pfizer’s Celebrex (celecoxib) and Merck’s Vioxx (rofecoxib) for common conditions like arthritis and painful menstruation. But what ultimately closed the deal for physicians was the publication of two major clinical trials, the Celecoxib Long-term Arthritis Safety Study in *JAMA* and the Vioxx Gastrointestinal Outcomes Research study in the *NEJM*. Both journal articles reassured physicians that COX-2 drugs triggered far fewer intestinal problems than did aspirin and the older, cheaper, off-patent over-the-counter painkillers. Celebrex became a blockbuster drug, and by 2000, 60 percent of Americans with arthritis were taking it. Worldwide, Vioxx was prescribed to over 80 million people.

What the advertisements did not mention and the journal articles tried at length to hide was the fact that Celebrex, Vioxx, and other COX-2 drugs were triggering heart attacks and strokes: the data that revealed the increased risks had been withheld from the submitted studies. When it discovered this, the *NEJM* published not one but two “expressions of concern” and an assailed Merck pulled Vioxx from the shelves in 2004.

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PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA (PhRMA) staff responded to three requests for a statement in response to this article by emailing a number of position statements, many taken from its website (<http://www.phrma.org>). One May 18 statement by PhRMA assistant general counsel Jeffrey Francer read in part:

PhRMA and its member companies support truthful, scientifically accurate promotional practices, as reflected in our Guiding Principles on Direct-to-Consumer Advertisements About Prescription Medicines and the PhRMA Code on Interactions with Healthcare Professionals. . . . In the end, by increasing healthcare providers' awareness of available treatment options, advertisements in medical journals—along with other types of communications—can enhance public health and improve patient care.

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HOW CAN JOURNALS best mitigate the flow of misinformation resulting from purchased bias, shrouded data, and statistical mischief? Some critics suggest that medical journals start by dispensing with pharmaceutical advertising altogether and instead accept other lucrative advertisers, like the makers of luxury goods. All the editors cited here think that ghostwriting should be banned outright, or they are, at least, like Bauchner, “very uncomfortable” with the practice.

“How to avoid corporate manipulation? That’s an easy question,” says Abramson. “Journals have to see the primary data. You cannot be irresponsible enough to publish an article and say that article has been through peer review when all the primary data and protocols haven’t been made available to you. Journals are blessing something with a public statement of integrity when there’s no way in hell they can know if it has any, so they’re playing a role in that deception.”

But what help exists for doctors, who need to know the potential sources of bias in peer-reviewed articles? Several books offer clear, impeccably researched guides to sniffing out manipulation. Angell’s *The Truth About the Drug Companies* and Abramson’s *Overdosed America* are likely to be most helpful to a busy clinician. The Pharmed-Out website (www.pharmedout.org) offers tools for detecting undue influence in medical research and publishing.

Leadership has also come from open-access journals, including the Public Library of Science publications. Their business models vary, but because they don’t accept pharmaceutical advertising or funding and are usually freely accessible to all online—in contrast to journals that must maintain income to answer to stockholders—open-access publishers can keep their hands in their pockets and avoid the rest of the profession’s rampant conflicts of interest. ●