

MEDICINE AND SOCIETY

CONFLICTS OF INTEREST — PART 2

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Understanding Bias — The Case for Careful Study

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In 1980, the *Journal's* editor Arnold Relman wrote an editorial entitled, “The New Medical-Industrial Complex.”¹ Although it’s hard to pinpoint the moment when a culture forever changed, the editorial represented a seminal event. Concerned about profiteering by private health care corporations, Relman wondered whether physicians could continue to honor their duty to serve as patients’ trustees. He argued that in order to represent patients’ interests fairly, physicians “should have no economic conflict of interest and therefore no pecuniary association with the medical-industrial complex.” Four years later, the *Journal* established an unprecedented rule that authors disclose their financial ties.²

Relman wanted to mitigate undue influence by curtailing physicians’ financial associations with companies, but his concern seemed as much about appearance as about reality. Noting the uncertainty about the magnitude of physicians’ financial stake in the medical marketplace, he wrote, “The actual degree of involvement is less important than the fact that it exists at all. As the visibility and importance of the private health care industry grows, public confidence in the medical profession will depend on the public’s perception of the doctor as an honest, disinterested trustee.” To ensure the primacy of public interests over those of industry stockholders, Relman called for two things: closer attention from the public and careful study.

In the ensuing decades, endless attention has been paid. Books have been written, with titles like *On the Take: How Medicine’s Complicity with Big Business Can Endanger Your Health* and, simply, *Bad Pharma*. A congressional inquiry has been undertaken. The Institute of Medicine (IOM) has published an exhaustive report, new rules have been implemented, and the media have covered any whiff of transgression. The recent passage of the Physician Payment Sunshine Act, requiring that

drug and device companies publicly disclose all physician payments over \$10, is the ultimate act of closer attention.

As for “careful study,” however, we still lack an empirical basis to guide effective conflict management. Although everyone agrees that patients’ health should not be compromised by physicians’ desire for financial gain, the extent to which physicians’ primary and secondary interests actually conflict, under what circumstances, and at what cost are unknown. Equally unclear are the benefits and harms of regulations aimed at exposing or mitigating these conflicts. The IOM’s 2009 review of conflict-of-interest policies recognized these limitations, noting that “on many topics related to conflicts of interest, no systematic studies are available. For other topics, data are suggestive rather than definitive.”³

THE EMPIRICAL GAP

Suggestive data may be worse than no data at all. Studies seeking evidence of industry influence usually find it, providing us with well-publicized associations. Some 94% of physicians have relationships with industry, though these interactions most often involve activities such as receiving drug samples or food in the workplace.⁴ Physicians who request a drug for hospital formulary are more likely than other physicians to have had drug company interactions.⁵ Industry-sponsored studies are more likely than government-sponsored ones to have positive results.⁶ Physicians who attend symposia funded by pharmaceutical companies subsequently prescribe the featured drugs at a higher rate.⁷ All these associations are probably valid. But they don’t answer the key question: Are any of these interactions, or efforts to curtail them, beneficial or harmful to patients?

It depends on how you define harm. Consider pharmaceutical “gifting,” a practice that smacks

of bribery — which may be sufficient reason to prohibit it. But does it actually hurt patients? According to one influential commentary, it does. The authors, who recommend banning various industry practices at academic medical centers, cite a review on gifting, noting that “an overwhelming majority of interactions had negative results on clinical care.”⁸

But that’s not actually what the review showed.⁹ First, the review makes clear that “no study used patient outcome measures.” Second, on some assessed outcomes, studies actually showed benefit, such as improved ability of physicians to identify a treatment for a complicated illness. And third, the measures with “negative outcomes,” suggesting compromised clinical care, included metrics such as “a positive attitude toward pharmaceutical representatives” and “rapid prescription of a new drug.” The review did link gifting to behaviors we should avoid, such as nonrational prescribing and decreased prescribing of generic drugs. But to use these data to conclude that such marketing practices are on balance harmful is to assume that increased prescribing of any drug is harmful.

Other types of industry interactions have also been cast as worrisome on the basis of suggestive extrapolations from data. Consider, for example, a 1998 study on the role of conflicts of interest in the debate over calcium-channel blockers.¹⁰ At the time, there was growing concern about the safety of these medications for the treatment of hypertension. The authors surveyed physicians to determine whether, among other things, those with financial ties to manufacturers of these drugs were more likely to publicly support their use. They were. But does that make their opinions suspect?

Although the authors note that their study doesn’t answer that question, they do wonder “how the public would interpret the debate over calcium-channel antagonists if it knew that most of the authors participating . . . had undisclosed financial ties with pharmaceutical manufacturers.” In this consideration, they were prescient. In today’s Sunshine era, patients naturally wonder whether they should question the prescriptions of doctors with industry ties. Unfortunately, although the study is widely cited by people seeking greater transparency, rarely mentioned is a critical fact: the physicians who favored the use of calcium-channel blockers were right.

Subsequent randomized trials demonstrated both the safety and efficacy of calcium-channel blockers, and they thus remain a common treatment for hypertension. Why is no light being shined on this relevant fact?

Perhaps because the reputational costs of suggesting that the influence of industry is not uniformly caustic are too high. Physicians know that “pharmascolds,” as physician-scientists David Shaywitz and Tom Stossel have dubbed them, will “vilify the medical products industry and portray academics working with it as traitors and sellouts.”¹¹ Although, by definition, a conflict of interest represents a risk that judgment will be compromised — not a determination that such a lapse has actually occurred — the pharmascolds’ narrative about conflicts of interest often conflates the two. Shaywitz and Stossel, who have each written on the benefits of academic–industry collaboration and the challenges of bringing new products to market, are rare voices competing with a loud chorus of shaming.

The result is a stifling of honest discourse and potential discouragement of productive collaborations. Several people I interviewed who had positive things to say about industry wished to remain anonymous. More strikingly, some of the young, talented physician-investigators I spoke with expressed worry about how any industry relationship would affect their careers. Would they be mocked or discredited when they gave talks? Would their patients trust them? Would they be able to write review articles and editorials?

In addition to potential deterrent effects of Sunshine-level transparency for physician-scientists considering industry collaborations, it remains unclear whether, for those who do engage, such disclosures actually mitigate the risk of bias. Work by psychologist George Loewenstein and colleagues suggests that the opposite may be true. One concern Loewenstein describes is a phenomenon called “moral licensing”: once disclosure gets the weight off your chest, you feel liberated and may feel licensed to behave immorally. A corollary concern is how disclosures affect their audience, who may interpret them as a sign of honesty and therefore feel more, rather than less, trusting. Finally, there’s some evidence that disclosures of financial ties by people serving in an advisory capacity may be interpreted as signs of expertise.¹²

As patients are increasingly encouraged to seek

information from their doctors about industry ties, the consequences of disclosure will be multi-layered, with each layer worthy of better understanding. But I think there's a deeper question, related not to the act of disclosure but to the substance of what is disclosed. What are we really looking for by illuminating physician–industry interactions? Are we looking in the right place? Might what really matters, to science and to patients, lie somewhere else — but be harder to see?

NONFINANCIAL BIASES

During my cardiology training, overnight call often entailed triaging phone calls from physicians from outside hospitals hoping to transfer a patient with ST-segment elevation myocardial infarction to our care. These cases could be tricky. Absent contraindications, guidelines recommend that hospitals lacking capability for percutaneous coronary intervention (PCI) treat such patients with fibrinolytics, after considering several factors including symptom duration and anticipated lag time between the patient's arrival at the first hospital and receipt of PCI at the second hospital.¹³ But it's impossible to predict how long a transfer will take. Sometimes you get magic — the transfer is initiated immediately, transport is rapid, and the catheterization team is ready and waiting. But often there are delays. So when I thought transfer might be delayed, I would ask the referring doctor whether thrombolytic therapy had been considered.

I would like to say I was just following the guidelines, that I'd read the many trials addressing the optimal approach to reperfusion under these circumstances and was thinking only about the patient. But deep down, I know my assessment may have been clouded by a secondary interest, and it wasn't stock in the manufacturer of a fibrinolytic agent. Rather, it was sleep — an area where my own best interests were clear. If the patient received fibrinolytics and reperfusion was successful, I could admit him when he arrived and then go to bed; catheterization could wait until the next day. If, instead, he was transferred for PCI, by the time he was reperfused, settled in the coronary care unit, and I had pulled the catheter sheath as required a few hours after the procedure, the night would be over.

Whether our judgments are motivated by fatigue, hunger, institutional norms, the diagno-

sis of the last patient we saw, or a memory of a patient who died, we are all biased in countless subtle ways. Teasing out the relative effects of any of these other biases is nearly impossible. You can't exactly randomly assign some physicians to being motivated by the pursuit of tenure, others by ideology, others by the possibility of future stock returns, and others by just wanting to be really good doctors. The difficulty of measuring these other motivations, however, creates the problem that plagues many quality-improvement efforts: we go after only what we can count. It is easy to count the dollars industry pays doctors, but this ease of measurement obscures two key questions: Does the money introduce a bias that undermines scientific integrity? And by focusing on these pecuniary biases, are we overlooking others that are equally powerful?

THE BIAS BLIND SPOT

In an appendix to the 2009 IOM report,¹⁴ Jason Dana, a psychologist now at Yale, discusses the relevance of psychology research to understanding and managing conflicts of interest. Dana emphasizes the “self-serving bias”: when we stand to gain from reaching a certain conclusion, we unwittingly assimilate evidence in a way that favors that conclusion. This tendency has been aptly described by psychologist Tom Gilovich,¹⁵ who explains that when evaluating conclusions we find agreeable, we ask ourselves, “Can I believe this?,” whereas when we face disagreeable conclusions we ask, “Must I believe this?”

In this framework, the primary objection to financial conflicts is that they cause us to err on the side of “Can I believe this?” In industry-funded studies, the concern is that investigators will look at equivocal data and interpret them in favor of the product. Physicians will hear an industry-sponsored talk and start prescribing a costly therapy that's no better than a generic alternative. A guideline-committee member reviewing evidence for a therapy made by a company that has supported his or her research will fail to recognize flawed methods. We can all cite stories, and some data, suggesting that these concerns are warranted. But does that mean that there's a systematic “Can I believe this?” bias in all matters industry-related?

Perhaps the danger lies as much in the “Must I believe?” stance advocated by people seeking

to discredit industry as in the “Can I believe?” introduced by industry ties. Dana notes that a major challenge in managing financial conflicts is that alerting people to their biases does little to mitigate their influence. Paradoxically, such education tends instead to make us even more confident in our own judgment but quicker to find bias in others — a phenomenon that Dana calls the “bias blind spot.”¹⁴ Studies suggest that we’re far more likely to think that drug promotions influence our colleagues than that they affect our own behavior.¹⁶

Dana invokes the bias blind spot to highlight the difficulty of managing financial conflicts through education and awareness, but couldn’t it be as relevant to people seeking to eliminate industry ties as to those who have them? Industry critics often insist that physicians who deny that financial stakes influence their judgment are merely unconscious of their bias and that therefore their relationships must be regulated. But couldn’t industry critics’ blind spots leave them unjustifiably confident that despite their industry aversion, they are bias-free?

It seems to me that anti-industry bias drives a “Must I believe?” approach to anything with industry involvement. Richard Epstein, a University of Chicago law professor who writes convincingly about the dangers of overregulating medical conflicts, questions certain limitations on the financial ties of FDA advisory-panel members. Although Epstein acknowledges that no one with a direct financial stake in a product should participate in its regulatory review, the general ban on industry ties introduces its own bias: “The scientists who have no such connections could easily harbor strong beliefs that new and risky drugs should be kept off the market which, in turn, could lead them to overstate the risks and understate the benefits of these new treatments.” When we study whether people with financial ties are more likely to vote in favor of a product, shouldn’t we also ask whether those without such ties are more likely to vote against it?¹⁷

How could an anti-industry bias affect clinical care? Let’s say your mother, 85 and intending to live to 100, has severe aortic stenosis. Her coexisting conditions make traditional aortic valve replacement too high risk, but she’s a good candidate for percutaneous transcatheter aortic valve replacement (TAVR). She’s admitted in heart failure to a coronary care unit where there are two

attending. One conducts research on aortic valve disease, sometimes supported by the manufacturer of a widely used transaortic valve. The other is an influential “thought leader” who has voiced strong opposition to overly aggressive end-of-life care and has argued that industry payments to physicians contribute to medical waste and rising drug costs. Both approach the weighing of the risk and benefits of TAVR with a point of view, but only one viewpoint has been flagged as potentially harmful and deserving of heightened scrutiny. And yet which physician would you choose for your mother?

Although some of these concerns are theoretical, evidence suggests that a “Must I believe?” mentality colors our interpretation of industry-sponsored research. In a 2012 study, Kesselheim and colleagues investigated how information about funding sources affects internists’ evaluation of clinical trial data.¹⁸ Physicians were given abstracts of fake drug studies, identical save for the funding source. Some abstracts gave no funding-source information, some listed National Institutes of Health (NIH) support, and some noted industry sponsorship. Disclosure of industry funding significantly affected physicians’ interpretation of data, and not favorably. Though the study methods were identical, physicians deemed rigorously conducted industry-sponsored studies to be less well-conducted than NIH-funded comparators. They were thus less likely to view them as important or to desire to read the entire article, and less inclined to prescribe the drugs in question.

In 1993, Kenneth Rothman, who’d been on the *Journal’s* editorial board when Relman issued the first conflict-of-interest policy, wrote a commentary arguing that using financial disclosures as a means of maintaining scientific objectivity was hypocritical.¹⁹ “These policies of mandatory disclosure thwart the principle that a work should be judged solely on its merits,” he wrote. “By emphasizing credentials, these policies foster an ad hominem approach to evaluating science.”

The study by Kesselheim et al. suggests that Rothman’s prophecy may have come true. So why, despite such reasoned cautions, have so few been willing to listen?

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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