Conflicts of Interest in Medicine: Why it's time for a UK Sunshine Act

Should doctors with commercial interests lead research on their products? Should we forget 'conflicts' and discus 'declarations of interest' instead? Who should hold and maintain conflicts of interest registers for doctors? Should practicing doctors work with the pharma industry as well as serve on guideline committees? Should researchers with extensive financial interests be disqualified from studies of their own products?

Prof. Carl Heneghan
Director of CEBM and Programs in Evidence-Based HealthCare
University of Oxford

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D., AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

ABSTRACT

Background Each year, clinical upper gastrointestinal events occur in 2 to 4 percent of patients who are taking nonselective nonsteroidal antiinflammatory drugs (NSAIDs). We assessed whether rofecoxib, a selective inhibitor of cyclooxygenase-2, would be associated with a lower incidence of clinically important upper gastrointestinal events than is the nonselective NSAID naproxen among patients with rheumatoid arthritis.

Methods We randomly assigned 8076 patients who were at least 50 years of age (or at least 40 years of age and receiving long-term glucocorticoid therapy) and who had rheumatoid arthritis to receive either

NONSTEROIDAL antiinflammatory drugs (NSAIDs) are among the most commonly used medications in the world.[1] A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15 to 30 percent of patients who regularly take NSAIDs,[2] the chief concern is clinically important gastrointestinal problems, such as bleeding. It has been estimated that more than 100,000 patients are hospitalized and 16,500 die each year in the United States as a result of NSAID-associated gastrointestinal events.[3,4]

Most NSAIDs inhibit both cyclooxygenase-1 and

Merck - Vioxx: VIGOR's Michael Weinblatt; well done, good and faithful servant

In 1999, Merck appointed rheumatologist Michael Weinblatt of Brigham & Women's Hospital in Boston to head the safety panel for the Vioxx VIGOR study.

When he became chair of the safety panel, Weinblatt and his wife owned $73,000 of Merck stock.

David Bjorkman, now dean of the University of Utah School of Medicine, also served on the five-member safety panel.

In 1999, he participated in the Merck speakers bureau and gave presentations in the summer of that year.

In addition, the panel meetings had a Merck employee present. The employee attended all the panel's meetings -- including its private deliberations. She even wrote the meetings' minutes.

The study showed that rofecoxib was not more effective in relieving symptoms of rheumatoid arthritis but did halve the risk of gastrointestinal events.

However, there was also evidence of an increased risk of myocardial infarction (relative risk 5.00, 95% confidence interval 1.68 to 20.13).

When this result was circulated internally at Merck, Edward Scolnick, the company's chief scientist, wrote in an email to colleagues about the cardiovascular risk: “It is a shame but it is a low incidence and it is mechanism based as we worried it was

The published VIGOR study obscured the cardiovascular risk associated with rofecoxib in several ways.

- Interim analysis had different termination dates: GI events were counted for 1 month longer than the CV events.
- 3 additional MIs occurred in the rofecoxib group in the month after
- Harm further minimised by a post hoc subgroup analysis on “indication for aspirin prophylaxis”;
- Presented the hazard of MI as if naproxen was the intervention group (relative risk 0.2, 0.1 to 0.7) and without reporting the absolute number of CVD events, even though all other results were presented appropriately with rofecoxib as the intervention group.
- The authors proposed a naproxen hypothesis, suggesting that rofecoxib had not been harmful but that naproxen had been protective.

At its last meeting, in December 1999, when the safety panel decided the heart problems weren't serious enough to stop the study, it also said that the problems merited analysis. The panel asked Merck to do that as soon as possible.

Merck sent back word that it wanted to wait.

When the safety panel's chairman Michael Weinblatt insisted, Merck proposed a plan.

The company would analyze heart problems it was told about by a "cutoff" date -- one month before the study ended.

Weinblatt agreed.

As a result of that cut-off date, three of the 20 heart attacks among Vioxx patients weren't included when Merck wrote up the study in the New England Journal of Medicine.

And, Vioxx looked safer than it really was.

Soon after agreeing to Merck's plan, Weinblatt signed a new consulting contract to sit on a Merck advisory board. Merck agreed to pay him $5,000 a day for 12 days over a two-year period.

Weinblatt received an initial check for $15,000 a few weeks later.

Research published in the medical journal The Lancet estimates that between 1999 and 2004, when Vioxx was withdrawn from the market, 88,000 Americans had heart attacks from taking the drug, and 38,000 of them died.

and especially after the FDA advisory committee meeting in 2001 — Merck issued a relentless series of publications, beginning with a press release on May 22, 2001, entitled “Merck Reconfirms Favorable Cardiovascular Safety of Vioxx” and complemented by numerous papers in peer-reviewed medical literature by Merck employees and their consultants. The company sponsored countless continuing medical “education” symposiums at national meetings in an effort to debunk the concern about adverse cardiovascular effects. The message that was duly reinforced was that rofecoxib had no cardiovascular toxicity: rather, naproxen was cardioprotective. Only by happenstance, in a trial involving 2600 patients with colon polyps

JAMA Blasts Vioxx Ghostwriters, Guest Authors, and Mortality Reporting

April 15, 2008
by Janis Kelly

NEW YORK CITY and SEATTLE, Washington—Two papers published in the April 16 Journal of the American Medical Association mine the trove of court documents from rofecoxib (Vioxx®, Merck & Co, Inc) lawsuits and give unflattering views of Merck's roles in manuscript preparation for clinical trial reports and in communicating information about rofecoxib-associated mortality risk. All but one of the authors of the 2 papers served as paid consultants for plaintiffs in litigation against Merck.

"This has occurred because physicians have allowed it to happen, and it is time to stop."—Catherine D. DeAngelis, MD, MPH, and Phil B. Fontanarosa, MD, MBA.

Joseph S. Ross, MD, MHS, of Mount Sinai School of Medicine, NY, and colleagues conclude that many, if not most, rofecoxib clinical trials reports were written by Merck scientists or ghostwritten by Merck-paid contract workers, then disguised with the names of academically affiliated doctors recruited as named authors.[1]

Bruce M. Psaty, MD, PhD, and Richard A. Kronmal, PhD, both from the University of Washington in

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Meeting Highlights

ISEMIR 2009: Video coverage of the Meeting

Physicians and the Pharmaceutical Industry

Is a Gift Ever Just a Gift?

Ashley Wazana, MD

Context Controversy exists over the fact that physicians have regular contact with the pharmaceutical industry and its sales representatives, who spend a large sum of money each year promoting to them by way of gifts, free meals, travel subsidies, sponsored teachings, and symposia.

Objective To identify the extent of and attitudes toward the relationship between physicians and the pharmaceutical industry and its representatives and its impact on the knowledge, attitudes, and behavior of physicians.

Data Sources A MEDLINE search was conducted for English-language articles published from 1994 to present, with review of reference lists from retrieved articles; in addition, an Internet database was searched and 5 key informants were interviewed.

Study Selection A total of 538 studies that provided data on any of the study questions were targeted for retrieval, 29 of which were included in the analysis.

Data Extraction Data were extracted by 1 author. Articles using an analytic design were considered to be of higher methodological quality.

Data Synthesis Physician interactions with pharmaceutical representatives were generally endorsed, began in medical school, and continued at a rate of about 4 times per month. Meetings with pharmaceutical representatives were associated with requests by physicians for adding the drugs to the hospital formulary and changes in prescribing practice. Drug company–sponsored continuing medical education (CME) preferentially highlighted the sponsor's drug(s) compared with other CME programs. Attending sponsored CME events and accepting funding for travel or lodging for educational symposia were associated with increased prescription rates of the sponsor's medication. Attending presentations given by pharmaceutical representative speakers was also associated with nonrational prescribing.

Conclusion The present extent of physician-industry interactions appears to affect prescribing and professional behavior and should be further addressed at the level of policy and education.

JAMA. 2000;283:373-380 www.jama.com

THERE ARE FEW ISSUES IN MEDICINE that bring clinicians into heated discussion as rapidly as the interaction between the pharmaceutical industry and the medical profession.[1-4] More than $11 billion is spent each year by pharmaceutical companies in promotion and marketing, $5 billion of which goes to sales representatives.[5,6] It has been estimated that $8000 to $13 000 is spent per year on each physician.[7,8] The attitudes about this expensive interaction are divided and contradictory. One study[9] found that 85% of medical students believe it is improper for politicians to accept a gift, whereas only 46% found it improper for themselves to accept a gift of similar value from a pharmaceutical company. Most medical associations have published guidelines to address this controversy. Perhaps the intensity of the discussion is related to the potential consequences were it confirmed that gifts influence prescription of medication that results in increasing cost or negative health outcomes.

This article addresses the question by way of a critical examination of the evi-

SPECIAL ARTICLE

Of Principles and Pens: Attitudes and Practices of Medicine Housestaff toward Pharmaceutical Industry Promotions

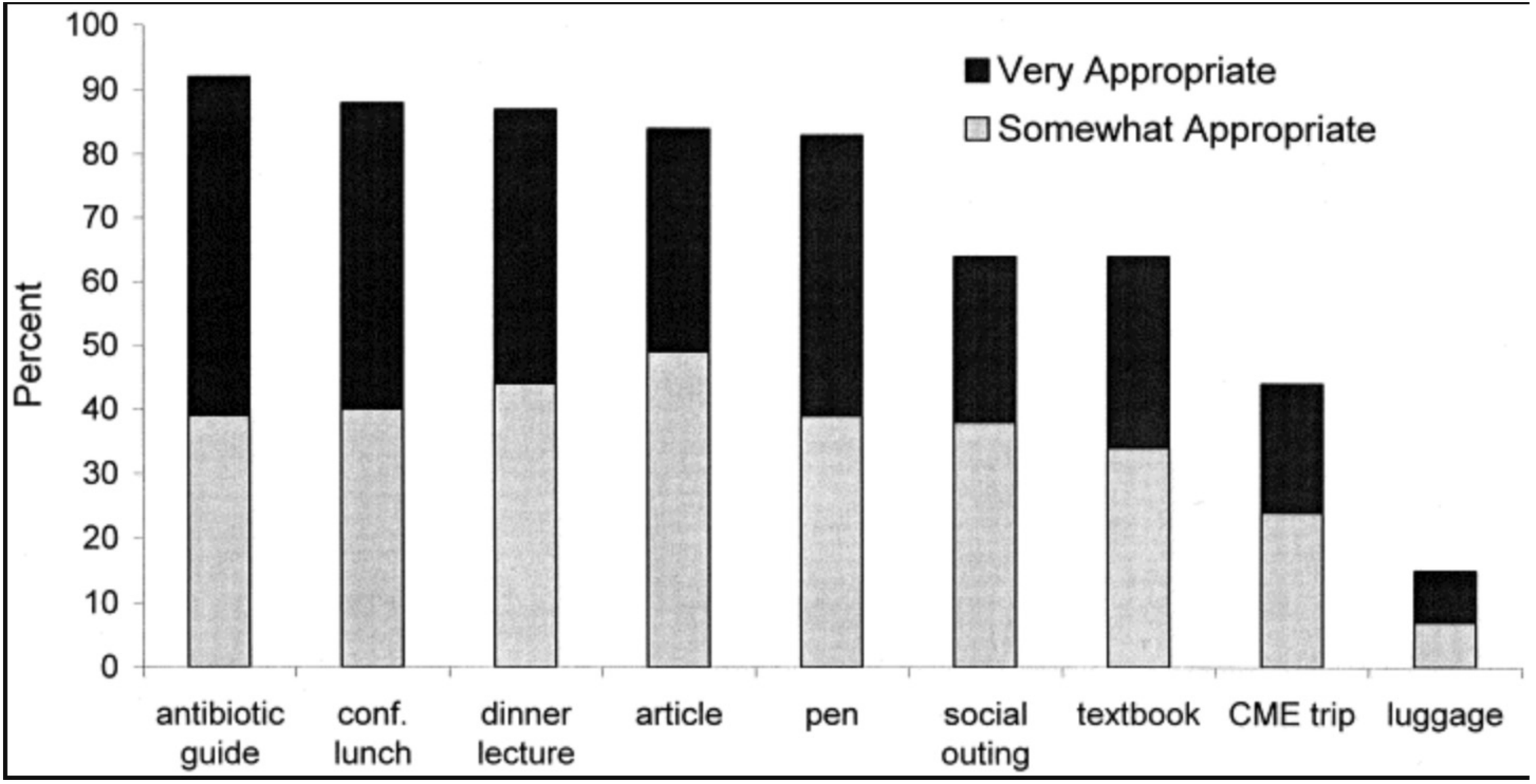
Michael A. Steinman, MD, Michael G. Shlipak, MD, MPH, Stephen J. McPhee, MD

PURPOSE: Little is known about the factors that influence housestaff attitudes toward pharmaceutical industry promotions or, how such attitudes correlate with physician behaviors. We studied these attitudes and practices among internal medicine housestaff.

SUBJECTS AND METHODS: Confidential surveys about attitudes and behaviors toward industry gifts were distributed to 1st- and 2nd-year residents at a university-based internal medicine residency program.

RESULTS: Ninety percent of the residents (105 of 117) completed the survey. A majority of respondents considered seven of nine types of promotions appropriate. Residents judged the appropriateness of promotions on the basis of their cost (median percentage of items considered appropriate 100% for inexpensive items vs. 60% for expensive ones) more than on the basis of their educational value (80% for educational items vs. 75% for noneducational ones; $P < .001$ for comparison of appropriateness based on cost vs. educational value). Behaviors were often inconsistent with attitudes; every resident who considered conference lunches ($n = 13$) and pens ($n = 18$) inappropriate had accepted these gifts. Most respondents (61%) stated that industry promotions and contacts did not influence their own prescribing, but only 16% believed other physicians were similarly unaffected ($P < .0001$). Nonetheless, more than two thirds of residents agreed that it is appropriate for a medical institution to have rules on industry interactions with residents and faculty.

CONCLUSIONS: Residents hold generally positive attitudes toward gifts from industry, believe they are not influenced by them, and report behaviors that are often inconsistent with their attitudes. Thoughtful education and policy programs may help residents learn to critically appraise these gifts. **Am J Med. 2001;110:551–557.**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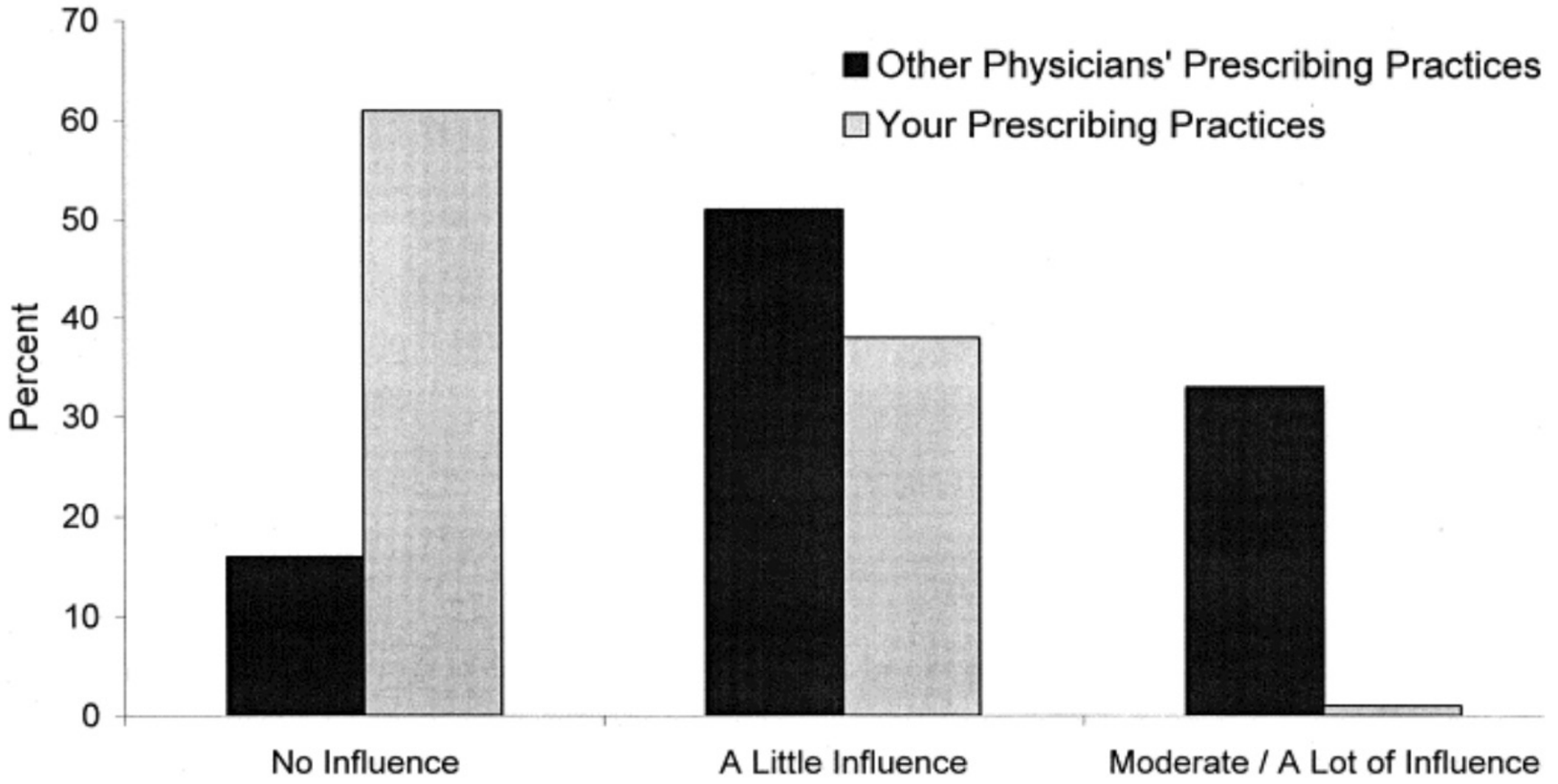

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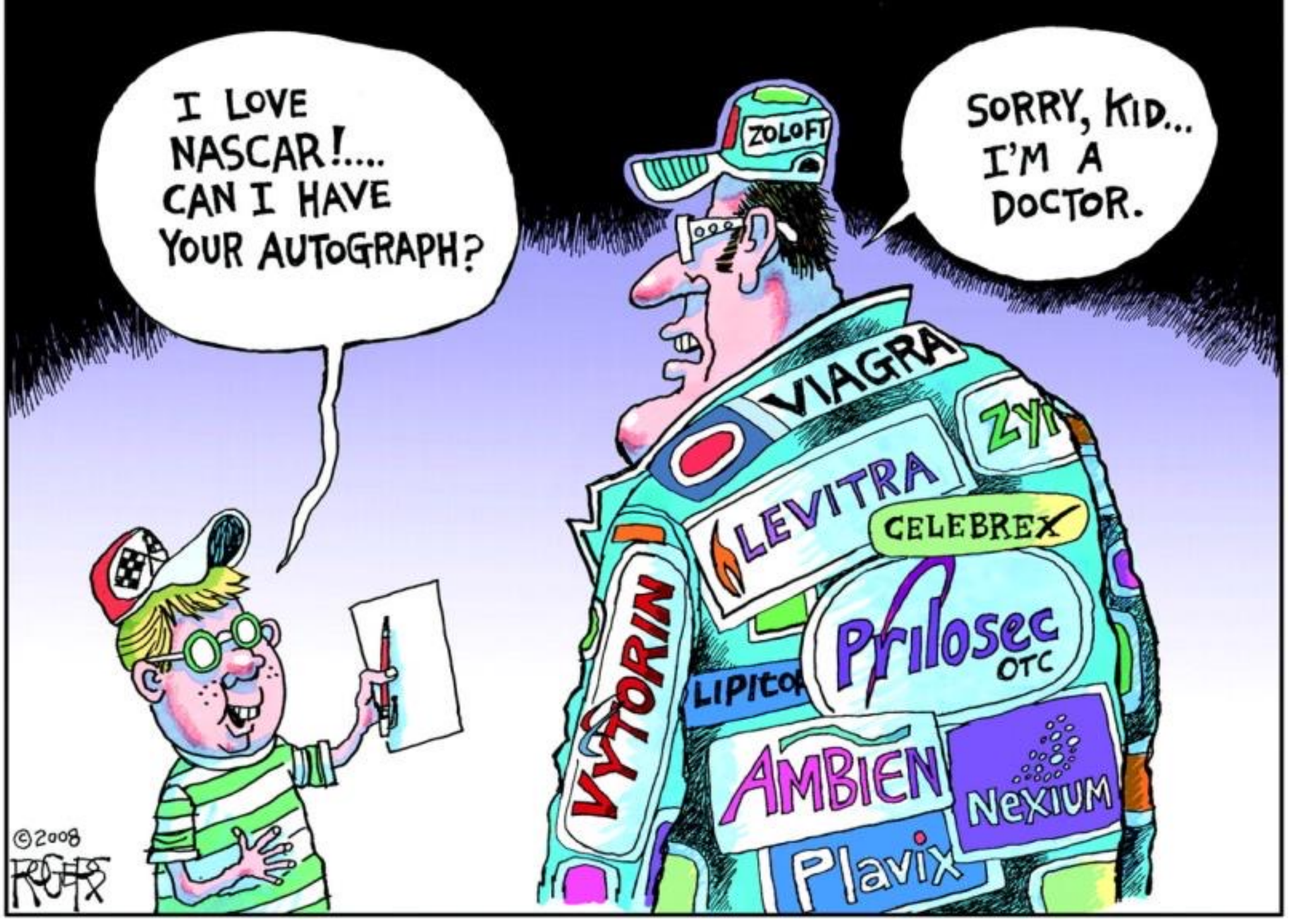
Figure 3. Perceived influence of pharmaceutical representatives on prescribing practices. Percentage of residents ($N = 102$) who believe that pharmaceutical representatives influence the prescribing practices of other physicians (dark bars) and influence their own prescribing practices (light bars). Residents perceive themselves as less prone to influence than are other physicians ($P < .0001$ by McNemar's chi-square test).


I LOVE NASCAR!.... CAN I HAVE YOUR AUTOGRAPH?
SORRY, KID... I'M A DOCTOR.
ZOLOFT
VIAGRA
ZYR
LEVITRA
CELEBREX
VYTORIN
LIPITOR
Prilosec OTC
AMBIEN
Nexium
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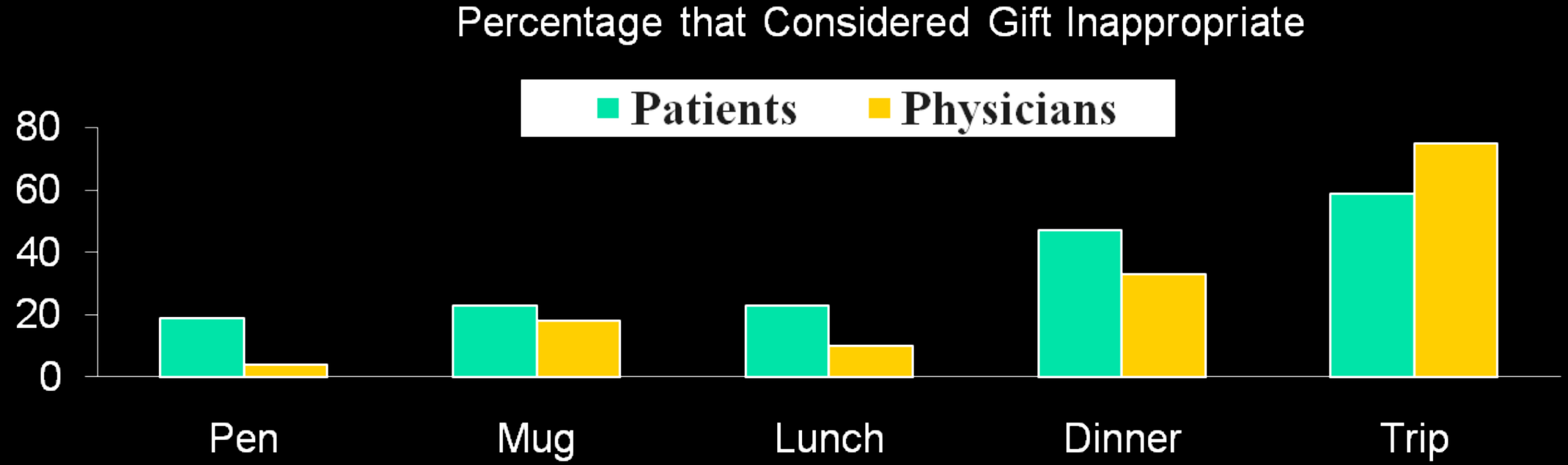
Pharmaceutical Branding of Residents

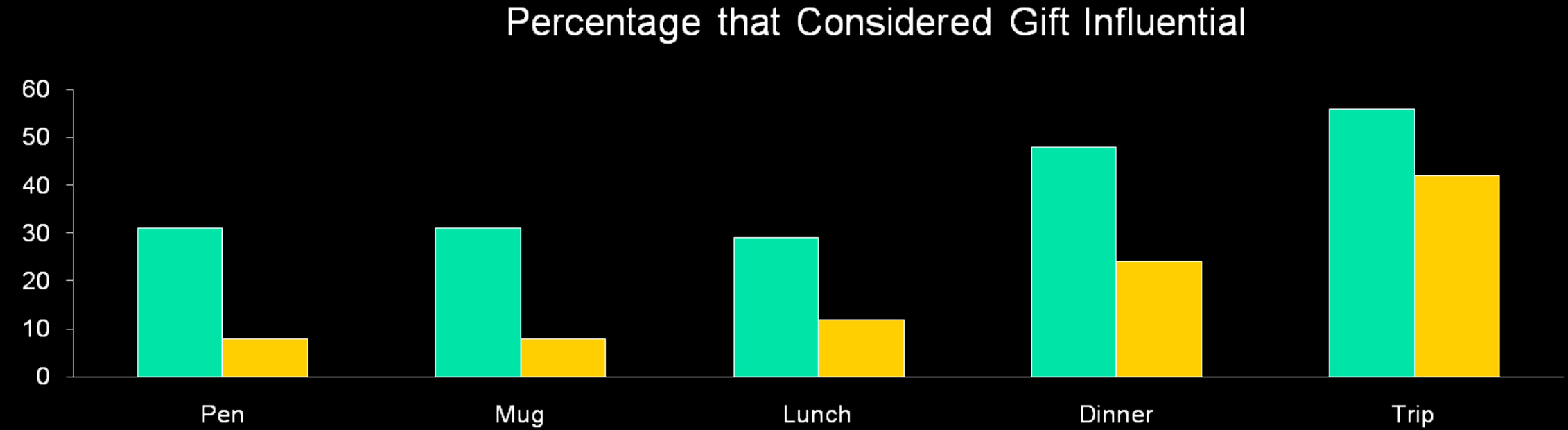
Table. Frequency of Items Found in Residents' White Coats

Item	No. (%) of Residents	
	Carrying the Item	Carrying the Item With a Pharmaceutical Brand
Reflex hammer	67 (41)	21 (31)
Calculator	95 (58)	13 (14)
Datebook	71 (43)	19 (27)
Calipers	46 (28)	39 (85)
Stethoscope tag	155 (95)	86 (55)
Penlight	84 (51)	38 (45)
Pens	161 (98)	127 (79)
Information cards	105 (64)	73 (70)
Reference books	152 (93)	137 (90)

Sigworth SK, Nettleman MD, Cohen GM. Pharmaceutical branding of resident physicians. JAMA. 2001;286:1024-5.

Physician vs. Patient Attitudes





Gibbons RV, Landry FJ, Blouch DL, Jones DL, Williams FK, Lucey CR, Kroenke K. A comparison of physicians' and patients' attitudes toward pharmaceutical industry gifts. J Gen Intern Med. 1998;13:151-4

- Gifts of **any size** influence behavior
  - According to Katz et al., "When a gift or gesture of any size is bestowed, it imposes on the recipient a sense of indebtedness. The obligation to directly reciprocate, whether or not the recipient is conscious of it, tends to influence behavior. . . . Feelings of obligation are not related to the size of the initial gift or favor"[1]

- Nevertheless, most physicians falsely believe that gifts could not influence their behavior[2]

[1]Katz D, Caplan AL, Merz JF. All gifts large and small: toward an understanding of the ethics of pharmaceutical industry gift-giving. Am J Bioeth. 2003;3:39-46

[2]Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift

Review

Why Review Articles on the Health Effects of Passive Smoking Reach Different Conclusions

Deborah E. Barnes, MPH; Lisa A. Bero, PhD

Objective.—To determine whether the conclusions of review articles on the health effects of passive smoking are associated with article quality, the affiliations of their authors, or other article characteristics.

Data Sources.—Review articles published from 1980 to 1995 were identified through electronic searches of MEDLINE and EMBASE and from a database of symposium proceedings on passive smoking.

Article Selection.—An article was included if its stated or implied purpose was to review the scientific evidence that passive smoking is associated with 1 or more health outcomes. Articles were excluded if they did not focus specifically on the health effects of passive smoking or if they were not written in English.

Data Extraction.—Review article quality was evaluated by 2 independent assessors who were trained, followed a written protocol, had no disclosed conflicts of interest, and were blinded to all study hypotheses and identifying characteristics of articles. Article conclusions were categorized by the 2 assessors and by one of the authors. Author affiliation was classified as either tobacco industry affiliated or not, based on whether the authors were known to have received funding from or participated in activities sponsored by the tobacco industry. Other article characteristics were classified by one of the authors using predefined criteria.

Data Synthesis.—A total of 106 reviews were identified. Overall, 37% (39/106) of reviews concluded that passive smoking is not harmful to health; 74% (29/39) of these were written by authors with tobacco industry affiliations. In multiple logistic regression analyses controlling for article quality, peer review status, article topic, and year of publication, the only factor associated with concluding that passive smoking is not harmful was whether an author was affiliated with the tobacco industry (odds ratio, 88.4; 95% confidence interval, 16.4-476.5; $P<.001$).

Conclusions.—The conclusions of review articles are strongly associated with the affiliations of their authors. Authors of review articles should disclose potential financial conflicts of interest, and readers of review articles should consider authors' affiliations when deciding how to judge an article's conclusions.

JAMA. 1998;279:1566-1570

THE US Environmental Protection Agency (EPA),[1] the US Surgeon General,[2] the National Research Council/National Academy of Sciences,[3] and the International Agency for Research on Cancer[4] have all reviewed the scientific evidence regarding the health effects of exposure to environmental tobacco smoke. somewhat disconcerting that not all published review articles are reaching the same conclusion about the health effects of passive smoking, particularly when there is consensus in the scientific community that passive smoking is harmful. The goal of this study was to identify factors that might explain why review articles on the health effects of passive smoking are reaching different conclusions.

Several interrelated factors may influence the conclusions of review articles. First, the conclusions of review articles may vary depending on the quality of the review conducted. Review article quality is generally measured in terms of the degree to which a systematic strategy has been used to evaluate the evidence on a particular topic.[9-15] It is generally believed that reviews that have been conducted systematically are less likely to reach biased conclusions than those that have not.[9,11,15,16] For example, Antman et al[9] found that, for reviews of myocardial infarction treatment, the conclusions of unsystematic reviews were often inaccurate and out-of-date when compared with a systematic review.[9] Therefore, in the literature on passive smoking, review articles may be reaching different conclusions depending on their quality.

Another factor that may influence the quality of review articles, and therefore their conclusions, is whether they have been subject to peer review. Research conducted by us and by others has found that, for original research articles, the quality of articles published in peer-reviewed journals is superior to the qual-

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Table 3.—Relationship Between Article Conclusions and Author Affiliations

Article Conclusion	No. (%) of Reviews: Tobacco-Affiliated Authors (n = 31)	No. (%) of Reviews: Non–Tobacco-Affiliated Authors (n = 75)
Passive smoking harmful	2 (6)	65 (87)
Passive smoking not harmful	29 (94)	10 (13)
Significance	$\chi^2_1 = 60.69$; $P<.001$	

farction treatment, the conclusions of unsystematic reviews were often inaccurate and out-of-date when compared with a systematic review.[9] Therefore, in the literature on passive smoking, review articles may be reaching different conclusions depending on their quality.

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Table 4.—Factors Associated With Concluding That Passive Smoking Is Not Harmful to Health: Multiple Logistic Regression Analysis

Factors	Odds Ratio* (95% Confidence Interval)	*P* Value
Mean quality score (continuous)	1.5 (<0.1-67.5)	.83
Peer review status		
Non–peer reviewed vs peer reviewed	1.3 (0.3-5.4)	.70
Author affiliation		
Tobacco industry vs non–tobacco industry	88.4 (16.4-476.5)	<.001
Topic		
Lung cancer vs multiple health effects	1.6 (0.2-10.3)	.63
Heart disease vs multiple health effects	1.6 (0.2-14.7)	.67
Respiratory disorders vs multiple health effects	1.8 (0.3-11.9)	.56
Other health effects vs multiple health effects	4.6 (0.6-32.8)	.13
Year of publication (continuous)	1.1 (0.9-1.3)	.45

*Odds ratio corresponds to factors associated with concluding that passive smoking is not harmful.

Major initiatives and polices covering declarations of interests

LEGISLATION

1980: US Congress Bayh-Dole Act [1]
Required investigators to disclose financial conflicts to interested parties including regulators, institutional officials, and funding agencies.

2007: FDA Amendments Act [9]
Prohibits members of advisory committees from participating with financial interests

2012 US Sunshine Act [12]
Designed to increase transparency around the financial relationships between physicians, teaching hospitals and manufacturers

2015 Medicines Australia Code of Conduct [14]
Payment Reporting Starts October 1, 2015

2018: French Sunshine Act [20]
The Loi Bertrand establishes the Transparency in Healthcare database public accessibility

POLICIES and GUIDANCE

1993: NHS Employees [2]
It is an offence for employees corruptly to accept any gifts or consideration as an inducement or reward in the context of NHS employment.

1995: Objectivity in Research Guide [3] US investigators required to disclose to an official(s) designated by the institution a listing of Significant Financial Interests.

2000: Department of Health Guidance [4]
Collaborative partnerships with industry should includes a transparent approach to any sponsorship.

2000: House of Commons Health Committee [7]
Doctors, in **particular 'key opinion** leaders', should be obliged to declare significant sums or gifts received as hospitality.

Government Response [8]
Recommends a register of interests be maintained by the relevant professional body.

2000: World Medical Association's Declaration of Helsinki [5]
Principle 22, includes "sources of funding" among the items to be provided to research subjects.

2003: US Department of Health & Human Services Guideline [6]
Establishing criteria to determine what constitutes an institutional conflict of interest.

2009: Institute of Medicine [10]
Report on Conflict of interest in medical research, education, and practice published

2011:ABPI code [11]
Required pharmaceutical companies to disclose monetary value of support with a value of £250 or more – threshold removed in 2012

2013: FDA Guidance [13]
for clinical investigators, industry, and FDA staff published

2016: EFPIA Disclosure Code [15] EFPIA members required to report payments and other transfers of value made to healthcare professionals

2016: FDA. Guidance [16]
for the Public, FDA Advisory Committee Members, and FDA Staff

2017: EMA policy [17]
handling of competing interests of scientific committees' members and experts

2017: NHS England policy [18]
Managing conflicts of interest in the NHS

2018: NHS Health Research Authority's [19]
Sets out steps a research ethics committee could take to mitigate competing interest of researchers

1980 → 2019

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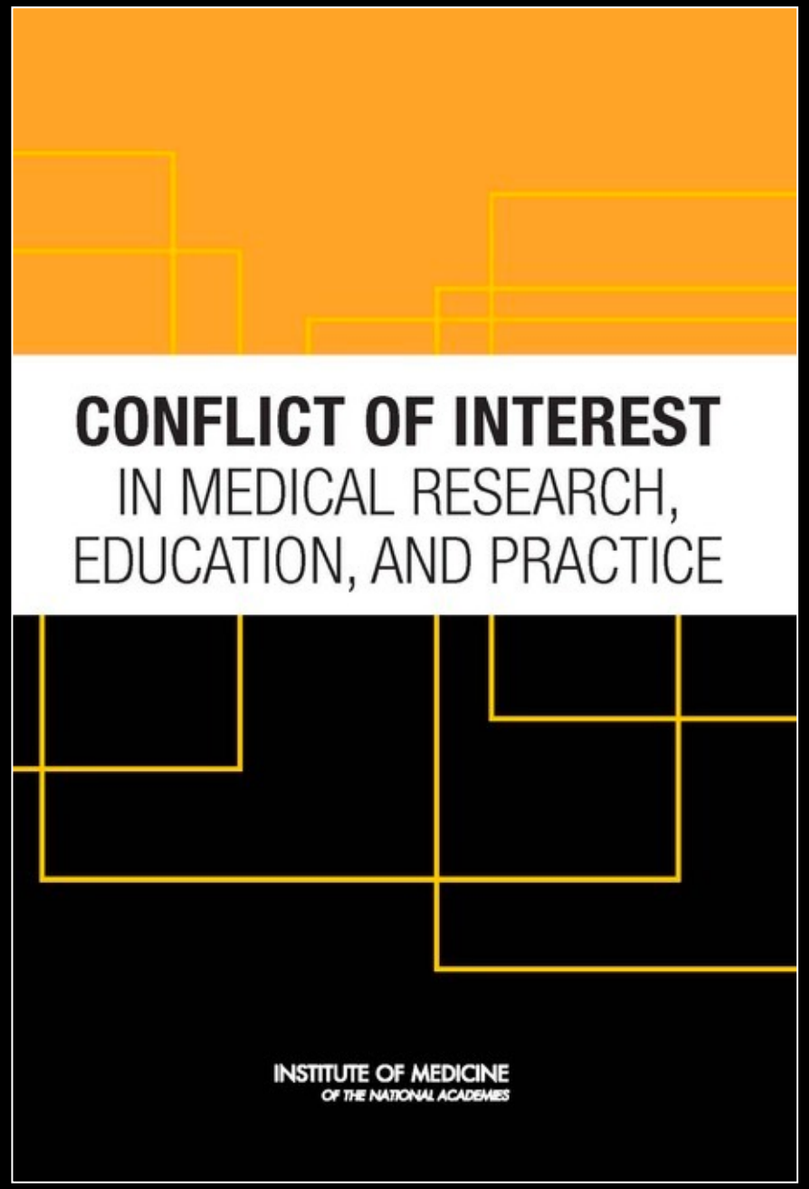
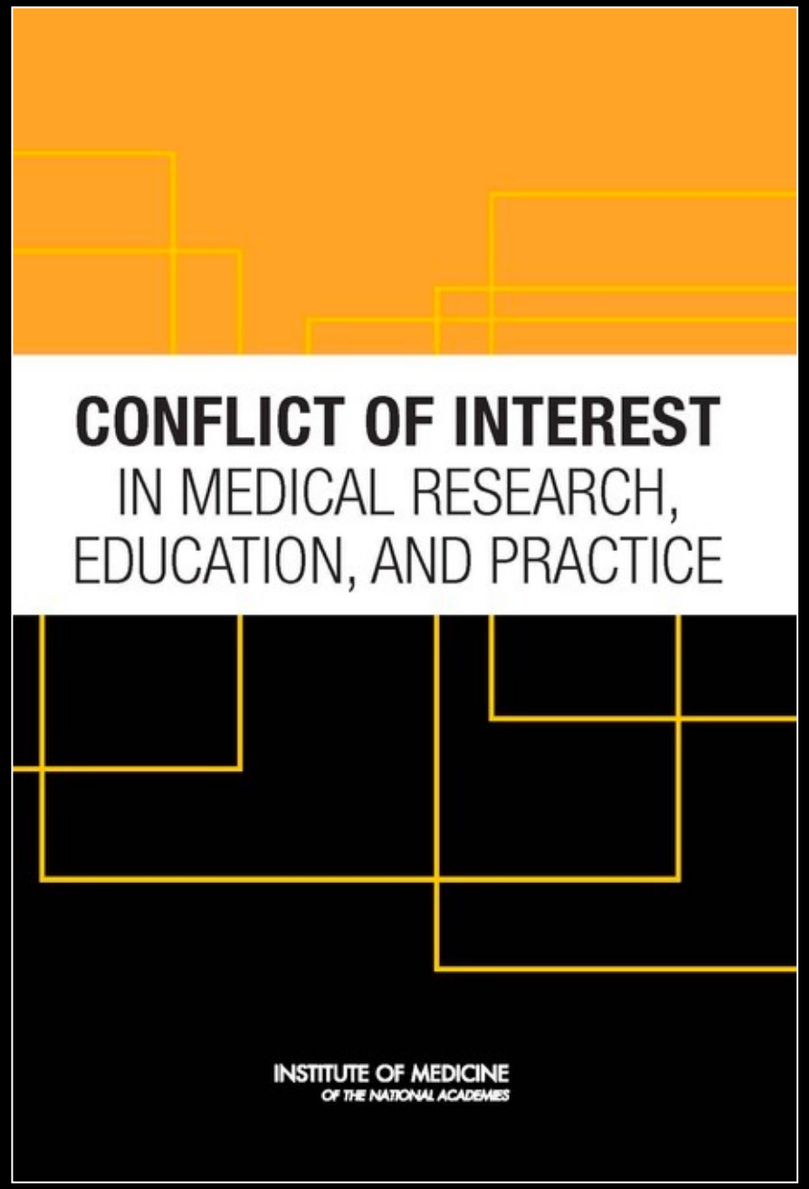
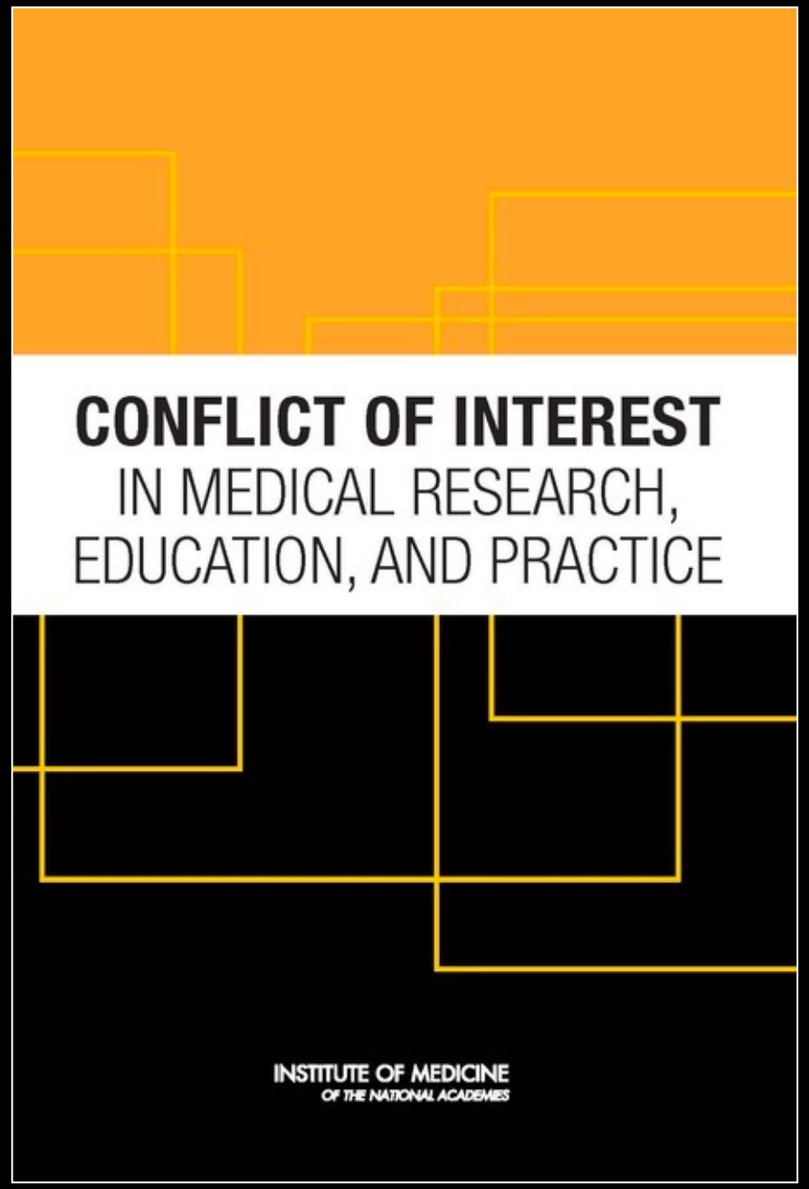


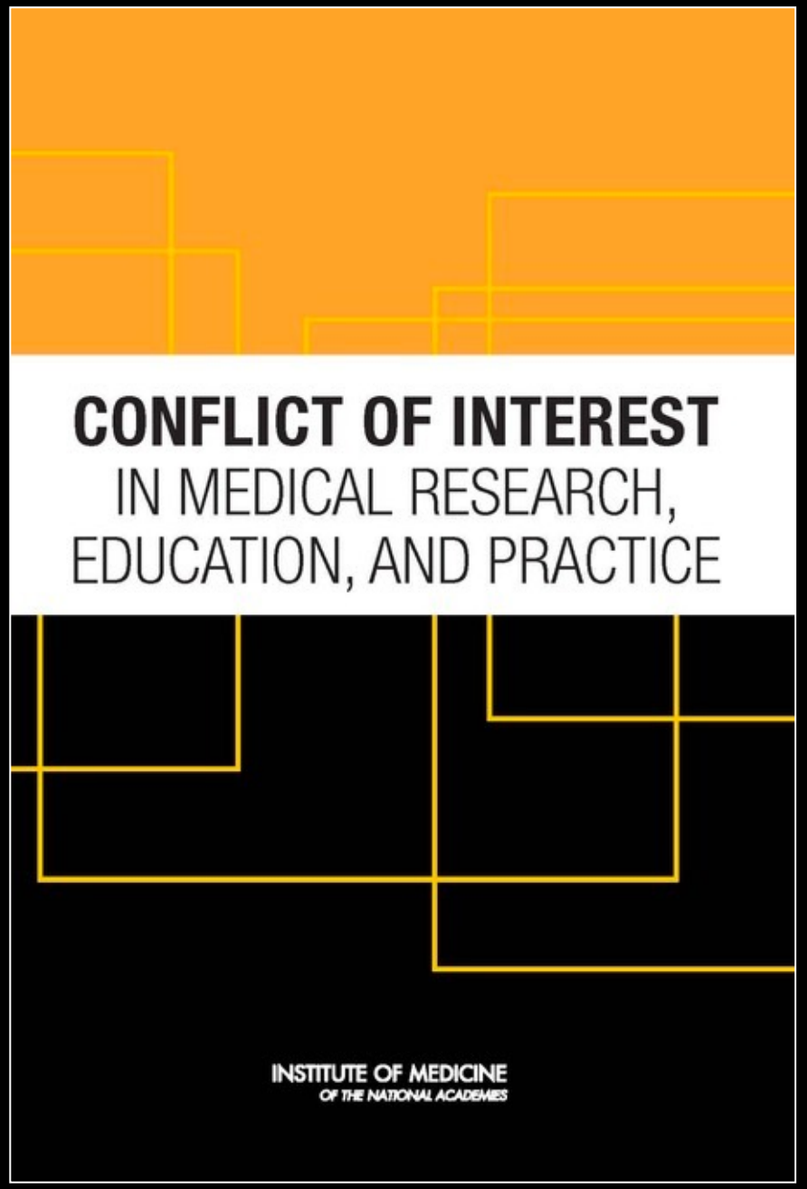
In 2007, the Institute of Medicine (IOM) appointed the Committee on Conflict of Interest in Medical Research, Education, and Practice to examine conflicts of interest in medicine and to recommend steps to identify, limit, and manage conflicts of interest without negatively affecting constructive collaborations



Although the committee recognizes that collaborations with industry can be beneficial, the committee recommends, as a general rule, that researchers should not conduct research involving human participants if they have a financial interest in the outcome of the research, for example, if they hold a patent on an intervention being tested in a clinical trial.



Acceptance of meals and gifts and other relationships with industry are also common among physicians who practice outside medical centers. Data suggest that these relationships may influence physicians to prescribe a company's medicines even when evidence indicates another drug would be more beneficial. Therefore, the committee recommends eliminating these problematic relationships between physicians and industry.



CONCLUSION there is growing concern among lawmakers, government agencies, and the public that extensive conflicts of interest in medicine require stronger measures. Responsible and reasonable conflict of interest policies and procedures will reduce the risk of bias and the loss of trust while avoiding undue burdens or harms and without damaging constructive collaborations with industry. Decisions about biomedical research, medical education, and patient care directly affect the public's health. The public needs to be able to trust that physicians' decisions are not inappropriately influenced by their financial relationships with industry

Major initiatives and polices covering declarations of interests

LEGISLATION

1980: US Congress Bayh-Dole Act [1]
Required investigators to disclose financial conflicts to interested parties including regulators, institutional officials, and funding agencies.

2007: FDA Amendments Act [9]
Prohibits members of advisory committees from participating with financial interests

2012 US Sunshine Act [12]
Designed to increase transparency around the financial relationships between physicians, teaching hospitals and manufacturers

2015 Medicines Australia Code of Conduct [14]
Payment Reporting Starts October 1, 2015

2018: French Sunshine Act [20]
The Loi Bertrand establishes the Transparency in Healthcare database public accessibility

POLICIES and GUIDANCE

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2000: Department of Health Guidance [4]
Collaborative partnerships with industry should includes a transparent approach to any sponsorship.

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2017: EMA policy [17]
handling of competing interests of scientific committees' members and experts

2017: NHS England policy [18]
Managing conflicts of interest in the NHS

2018: NHS Health Research Authority's [19]
Sets out steps a research ethics committee could take to mitigate competing interest of researchers

1980 → 2019

- The U.S. Physician Payment Sunshine Act/Open Payments is a federal law that requires all pharmaceutical, biologics and medical device manufacturers to disclose payments and transfers of value provided to U.S. physicians and teaching hospitals
- The Sunshine Act:
  - Makes interactions significantly more visible to the public
  - Covers only U.S. physicians and teaching hospitals
  - Applies to U.S. physicians regardless of the country where a payment or transfer of value occurs
- Manufacturers are required to submit Sunshine Act data to the Centers for Medicare and Medicaid Services (CMS) each year

Reporting Requirements

- All payments or transfers of value **over $10**
- Any payments made to another entity "at the request of" or "on behalf of" a physician or teaching hospital
- If, within a calendar year, a manufacturer makes payments to or provides a physician or teaching hospital **in excess of $100 in total**, then **all** payments and items of value provided during that calendar year must be reported (even if they are individually less than $10)
- A manufacturer is required to report research payments made to institutions conducting clinical research on the manufacturer's behalf, including the name(s) of the Principal Investigator(s), even if the manufacturer does not direct funds to those specific physicians

Types of payments or items of value that must be reported include:

- Consulting Payments and Honoraria
- Research & Clinical-Trial Related Expenditures
- Educational Items (*e.g.,* textbooks, journal article reprints)
- Educational and Research Grants
- Royalty Payments and Licensing Fees
- Expenses such as Travel, Lodging and Meals
- Training & Education Expenses
- Charitable Donations

DOLLARS FOR DOCTORS

Now There's Proof: Docs Who Get Company Cash Tend to Prescribe More Brand-Name Meds

The more money doctors receive from drug and medical device companies, the more brand-name drugs they tend to prescribe, a new ProPublica analysis shows. Even a meal can make a difference.

by Charles Ornstein, Mike Tigas and Ryann Grochowski Jones, March 17, 2016, 5 a.m. EDT

Table 3: High brand-name prescribing incidence rates for doctors who did and did not take industry payments

	Payments		No payments			95% CI	
	High p_brand (+)	High p_brand (−)	High p_brand (+)	High p_brand (−)	RR*	Lower	Upper
Family Medicine	6,114	40,639	1,212	17,686	2.04	1.92	2.16
Internal Medicine	4,334	31,995	768	14,510	2.37	2.20	2.56
Cardiology	1,865	10,443	98	1,411	2.33	1.92	2.84
Psychiatry	1,271	7,379	174	2,228	2.03	1.74	2.36
Ophthalmology	1,198	5,919	50	1,029	3.63	2.76	4.79

*All values statistically significant at 95% confidence.

Doctors who received payments were, in general, two times as likely to be high brand-name prescribers than doctors who did not receive payments.

by Charles Ornstein, Mike Tigas and Ryann Grochowski Jones, March 17, 2016, 5 a.m. EDT

Table 4: Very high brand-name prescribing incidence rates for doctors who did and did not take industry payments

	Payments		No payments			95% CI	
	Very high p_brand (+)	Very high p_brand (−)	Very high p_brand (+)	Very high p_brand (−)	RR*	Lower	Upper
Family Medicine	1,622	45,131	242	18,656	2.71	2.37	3.10
Internal Medicine	1,558	34,771	234	15,044	2.80	2.44	3.21
Cardiology	491	11,817	18	1,491	3.34	2.10	5.34
Psychiatry	367	8,283	46	2,356	2.22	1.64	3.00
Ophthalmology	156	6,961	9	1,070	2.63	1.35	5.13

*All values statistically significant at 95% confidence.

Doctors who received payments were two to three times as likely to have very high brand-name prescribing rates than those who did not receive payments.

Major initiatives and polices covering declarations of interests

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BMJ

BMJ 2014;348:g1301 doi: 10.1136/bmj.g1301 (Published 5 February 2014)

LETTERS

REGISTRY OF DOCTORS' COMPETING INTERESTS

Problems with ABPI proposals to release data on payments to doctors

Ben Goldacre *research fellow*

London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

Whitehead of the Association of the British Pharmaceutical Industry (ABPI) says the drug industry will soon declare all payments to doctors.[1 2] There are several problems with his new promises.

Firstly, industry has been promising such transparency for years, without delivering. At the same time, the same companies are campaigning against transparency in other areas.

Secondly, industry representatives now say—when directly questioned about completeness—that EU privacy law will permit individual doctors to opt out of having their payments declared. Some of the most important data will still be hidden.

Thirdly, doctors' potential conflicts of interest extend beyond payments from drug companies to include payments from PR firms, income from local healthcare providers, and more.

This is why we suggest that doctors should be obliged to declare their own complete list of competing interests, ideally to the General Medical Council.[1]

Greater transparency from the ABPI is still welcome. The limited, incomplete dataset it provides could be merged with other data sources to provide a more complete picture and help identify gaps that may signal areas and individuals of greater concern.

Unfortunately the ABPI currently plans to release this information through its own website. It says it wants to provide a "one stop" service with web pages for patients wishing to find out about their doctors. In reality, this will mean that a flawed and incomplete dataset is presented to the public, as if complete, under editorial control of industry, with better uses unnecessarily obstructed.

The ABPI could release this information as structured open data, in open formats, freely available for reuse by third parties, as is now standard practice in government and other sectors.[3] Its data could then be aggregated and matched against other sources to produce genuinely useful information and insights. The ABPI should reconsider.

Competing interests: I am a co-signatory to the initial letter calling for the GMC to run a competing interests database. I am a collaborator on a website allowing doctors to declare their own competing interests. I receive income from speaking and writing for lay audiences on problems in medicine, including competing interests.

Full response at: www.bmj.com/content/348/bmj.g236/rr/682926.

1 Whitehead S. ABPI efforts to increase transparency about competing interests. *BMJ* 2014;348:g1300.
2 McCartney M, Goldacre B, Chalmers I, Reynolds C, Mendel J, Smith S, et al. Why the GMC should set up a central registry of doctors' competing interests. *BMJ* 2014;348:g236. (15 January.).
3 Cabinet Office. Open Data: unleashing the potential. 2012. www.gov.uk/government/publications/open-data-white-paper-unleashing-the-potential.

Cite this as: *BMJ* 2014;348:g1301

Disclosure UK

The relationship between the pharmaceutical industry and healthcare professionals (HCPs) and healthcare organisations (HCOs) plays a vital role in the development and delivery of life-enhancing and life-saving medicines.

It is a relationship that we are proud of. At the core of the relationship is sharing knowledge to improve outcomes for patients. We want to ensure that patients and others have confidence that this relationship is open and transparent and this is why the pharmaceutical industry is taking the lead on disclosing details of payments and other benefits in kind made by industry to HCPs and HCOs.

This information will be published on the database - Disclosure UK.

Disclosure UK is part of a Europe-wide initiative to increase transparency between pharmaceutical companies and the doctors, nurses, pharmacists and other health professionals and organisations it works with.

BMJ Open

Disclosure of payments by pharmaceutical companies to healthcare professionals in the UK: analysis of the Association of the British Pharmaceutical Industry's Disclosure UK database, 2015 and 2016 cohorts

Shai Mulinari,[1] Piotr Ozieranski[2]

To cite: Mulinari S, Ozieranski P. Disclosure of payments by pharmaceutical companies to healthcare professionals in the UK: analysis of the Association of the British Pharmaceutical Industry's Disclosure UK database, 2015 and 2016 cohorts. *BMJ Open* 2018;**8**:e023094. doi:10.1136/bmjopen-2018-023094

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-023094).

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ABSTRACT

Objectives To analyse the section of Disclosure UK that pertains to healthcare professionals (HCPs) in order to provide insight into the database's structure and content and suggest ways to improve its transparency.

Design and participants Cohort study of drug companies and HCPs in the 2015 and 2016 versions of Disclosure UK.

Results Companies report transfers of value (ToVs) to named HCPs or, where an HCP declines to consent, in aggregate. Only a limited number of variables describe the recipient HCP and the ToV, precluding refined analyses. In 2015, 107 companies reported 54 910 ToVs worth £50 967 728. In 2016, 109 companies reported ToVs but spending decreased by 7.3%. The spending was concentrated: the top 10 spenders reported about 50% of the total value, with consultancy-related payments comprising over 70%, and the rest being costs for events. In 2015, 55.5% (30 478) of ToVs worth £24 428 619 (47.9%) were disclosed at the individual HCP level, increasing to 64.5% (32 407) and £28 145 091 (59.2%) in 2016. Despite increased individual-level disclosure in 2016, the median number of ToVs reported by each company at the individual level was only 57.7%, with 25% of companies reporting less than 38.6%. We found little agreement (62%–48% in 2015 and 46%–30% in 2016) between HCP consent rates that we calculated based on information in the database and those provided by companies.

Conclusions Key deficiencies in Disclosure UK include: insufficient information on payments and recipients, a relatively low HCP consent rate for individual-level disclosure, differences in consent rates across companies and payment types, and reporting ambiguities or inconsistencies. We employ these findings to develop recommendations for improving transparency, including an easily interpretable consent rate statistic that allows for comparison across years, firms and countries. If deficiencies remain unresolved, the UK should consider introducing legislation requiring mandatory disclosure to allow for adequate tracking of industry payments.

Strengths and limitations of this study

- Thus far, there have been no studies analysing publicly available pharmaceutical industry disclosure databases in any European country, including the UK.
- Our analysis was based on the full Disclosure UK dataset for healthcare professional (HCP) payments for two years.
- Our calculations of overall payment sums and HCP consent rates are consistent with what was reported by the Association of the British Pharmaceutical Industry, which corroborates our methodology.
- A limitation is that we had no way of checking the accuracy of the data reported by companies.
- Our study does not consider differences in companies' approaches to interpreting and reporting of some data elements and which can invalidate direct comparison of the value of payments between companies.

INTRODUCTION

Collaboration between pharmaceutical companies and healthcare professionals (HCPs) is seen by many as vital for boosting innovation and efficiency in healthcare. However, HCPs' commercial links create the potential for conflicts of interest[1] that may bias medical research,[2] treatment decisions[3] and lead to wasteful public spending.[4] In recent years, a key way of addressing these concerns[5] — and protecting the transparency and accountability of healthcare policy and practice[6] — is by enhancing the transparency in the industry's financial support to HCPs.[7] By far the most recognised transparency initiative globally is the US Government's Physician Payment 'Sunshine Act', requiring pharmaceutical and medical device companies to

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2016	2017	2018
£478,800.31	£95,493.27	£32,175.86

Reference	Company Name	Year	Joint Working Link	Joint Working	Donations, Grants, Benefits	Event Sponsorship	Event Reg. Fees	Event Travel And Acc.	Service Fees	Service Expenses	Total
1896629	Gilead	2018		£0.00	£0.00	£5,000.00	£0.00	£0.00	£0.00	£0.00	£5,000.00
1896630	Gilead	2018		£0.00	£0.00	£5,000.00	£0.00	£0.00	£0.00	£0.00	£5,000.00
1896631	Gilead	2018		£0.00	£0.00	£1,000.00	£0.00	£0.00	£0.00	£0.00	£1,000.00
1896632	Gilead	2018		£0.00	£0.00	£1,000.00	£0.00	£0.00	£0.00	£0.00	£1,000.00
2178181	GlaxoSmithKline plc	2018		£0.00	£0.00	£12,000.00	£0.00	£0.00	£0.00	£0.00	£12,000.00
2178182	GlaxoSmithKline plc	2018		£0.00	£0.00	£720.00	£0.00	£0.00	£0.00	£0.00	£720.00
2163742	Roche Products Limited	2018		£0.00	£0.00	£0.00	£0.00	£0.00	£3,455.86	£0.00	£3,455.86
2006202	UCB Pharma Ltd	2018		£0.00	£4,000.00	£0.00	£0.00	£0.00	£0.00	£0.00	£4,000.00

Major initiatives and polices covering declarations of interests

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1980 → 2019

2012: USA Sunshine Act: Designed to increase transparency around the financial relationships between physicians, teaching hospitals and manufacturers

2013 Portugal Sunshine Act: Ensure that all payments made by pharmaceutical companies to healthcare professionals and others in the healthcare sector are registered and visible.

2014 Denmark HCP Affiliation/Sunshine Act. To forward annually to the Danish Health and Medicines Authority details of all Health Care Practitioners affiliated with the company within the preceding year.

2015 Australia Medicines Australia Code of Conduct: For the first year, companies requested the agreement of the healthcare professionals received payments or educational support for their information to be published in a report. After 12 months of settling into the new system, the Code transitioned to mandatory reporting of these payments to healthcare professionals for member companies.

2017 South Korea Sunshine Act: Requires pharmaceutical and medical device companies operating in South Korea to prepare an aggregated expenditure report if they have provided economic benefits to healthcare professionals and others employed at medical institutions during a fiscal year.

2018 France Loi Bertrand: 'French Sunshine Act' establishes public accessibility To the Transparency in Healthcare database.

thebmj

BMJ 2019;367:l6236 doi: 10.1136/bmj.l6236 (Published 6 November 2019)

EDITORIALS

Check for updates

Declaring interests and restoring trust in medicine

We need a system wide strategy to record and manage conflicts of interest across healthcare

Carl Heneghan *professor*, Margaret McCartney *honorary fellow*

Centre for Evidence-Based Medicine, University of Oxford, Oxford, UK

There is a long history of individuals and organisations attempting to fix the biases that arise from conflicts of interests. Such conflicts contribute to a breakdown in research integrity[1] and lead to more favourable outcomes for sponsors,[2] the withholding of results,[3] and an overall lack of trust in research.[4]

Journals disclose authors' potential conflicts of interest to improve the objective assessment of research, increase its credibility, and make peer reviewers, editors, and readers aware of—and account for—the biases that conflicts induce. The International Committee of Medical Journal Editors (ICMJE) considers the purposeful failure to disclose conflicts of interest a form of misconduct. Whether disclosure influences peer reviewers' assessment of the quality of submitted research is, however, unclear.

In a linked paper, John and colleagues (doi:10.1136/bmj.l5896) tackled this issue by asking whether revealing authors' conflicts at peer review affects the quality rating of submitted manuscripts.[5] From a sample of 1480 research papers submitted to *Annals of Emergency Medicine*, peer reviewers were randomised to receive a full conflict of interest disclosure or no disclosure. Access to disclosures had no impact on reviewers' quality rating of research.

To many, this result might not be surprising. Little agreement exists on what constitutes effective peer review or the skills required to provide it,[6] and there is little evidence that peer review does what many think it should do—ensure the quality of research.[7] Although peer review is highly regarded by researchers and considered essential for publication of research[8] it has many flaws: In one study, 607 peer reviewers for *The BMJ* detected only one third of major errors inserted into test trial reports, despite training;[9] In another, 260 readers missed 95% of the 39 discrepancies in a clinical trial report.[10] Peer review itself is of questionable value and could offer false reassurance.

We don't know what should happen when conflicts of interest are disclosed to peer reviewers. It is currently unclear if disclosure identifies, reduces, or avoids biases in research, or if it simply creates false reassurance among reviewers and readers,[11] Estimating the impact of conflicts of interest is a difficult task.[12]

Goupil and colleagues (doi:10.1136/bmj.l6015) provide more tangible evidence that gifts from pharmaceutical companies to French general practitioners (GPs) might influence prescribing.[13] Their retrospective study, using data from the French Transparency in Healthcare and National Health Insurance databases, reports that GPs who received no gifts prescribed cheaper generic drugs and had better drug prescription efficiency indicators than those in receipt of gifts.

While these results are consistent with previous evidence,[14] they highlight the value of the Transparency in Healthcare database. Without it, gifts to French GPs from pharmaceutical companies would not be readily accessible for analysis.

The French "Sunshine Act" (The Loi Bertrand) established the Transparency in Healthcare database that became publicly accessible in 2018. The law requires health products companies to disclose agreements with healthcare providers publicly within 15 days. Any benefit to the healthcare provider exceeding a value of €10.00 (£8.60) in cash or in kind must be disclosed within six months.[15] Although no direct causal link was found between the gifts received and GP prescribing, Goupil and colleagues' study shows the importance of disclosure legislation: gifts to French GPs are common (36 232/41 257 GPs (87.8%) listed in the database had received gifts) and are associated with poorer prescribing practices and increased costs to the healthcare system.

The influence of organisational or individual conflicts on clinical practice demands a system-wide strategy to manage and mitigate such conflicts. Our current understanding of the effects of conflicts of interest is impeded by ineffective strategies to search for, report, and record them. Laws that mandate full transparency—with expectations on both individuals and industry to provide payment data—solve the problems associated with voluntary disclosure and might permit a more thorough understanding of the wide ranging impacts that conflicts of interest have across healthcare. Better data on conflicts would mean better research, a clearer understanding, and more coherent action to reduce harm—a process that might just restore some much needed trust in research.

Competing interests: CH receives funding support from the NIHR (National Institute for Health Research) School for Primary Care Research Evidence Synthesis

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BMJ Open

Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians' attitudes and prescribing habits: a systematic review

Freek Fickweiler, Ward Fickweiler, Ewout Urbach

To cite: Fickweiler F, Fickweiler W, Urbach E. Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians' attitudes and prescribing habits: a systematic review. *BMJ Open* 2017;**7**:e016408. doi:10.1136/bmjopen-2017-016408

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ABSTRACT

Objectives The objective of this review is to explore interactions between physicians and the pharmaceutical industry including sales representatives and their impact on physicians' attitude and prescribing habits.

Data sources PubMed, Embase, Cochrane Library and Google scholar electronic databases were searched from 1992 to August 2016 using free-text words and medical subject headings relevant to the topic.

Study selection Studies included cross-sectional studies, cohort studies, randomised trials and survey designs. Studies with narrative reviews, case reports, opinion polls and letters to the editor were excluded from data synthesis.

Data extraction Two reviewers independently extracted the data. Data on study design, study year, country, participant characteristics, setting and number of participants were collected.

Data synthesis Pharmaceutical industry and pharmaceutical sales representative (PSR) interactions influence physicians' attitudes and their prescribing behaviour and increase the number of formulary addition requests for the company's drug.

Conclusion Physician–pharmaceutical industry and its sales representative's interactions and acceptance of gifts from the company's PSRs have been found to affect physicians' prescribing behaviour and are likely to contribute to irrational prescribing of the company's drug. Therefore, intervention in the form of policy implementation and education about the implications of these interactions is needed.

Strengths and limitations of this study

- Large up-to-date systematic review of studies exploring the impact of pharmaceutical industry representative interactions on physicians.
- This systematic review used the recommendations outlined in the Cochrane Handbook for conducting systematic reviews and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the evidence by outcome.
- PubMed, Embase, Cochrane Library and Google Scholar electronic databases were searched from 1992, as well as grey literature.
- Most studies identified were observational and of varying methodological design.
- Some studies did not provide evidence for the significance of their findings.

PSRs may influence prescribing behaviour.[9–16] However, the evidence determining whether pharmaceutical industry and PSRs interactions influence physicians is divided and contradictory. Studies have indicated that physicians may be unable to distinguish between promotional information and scientific evidence.[17 18] Physicians, however, believe their colleagues are more susceptible to pharmaceutical industry marketing strat-

Table 2 Impact of physician–pharmaceutical industry interaction on physician

#	Attitudes	Prescribing behaviour	Knowledge	Formulary requests	Quality of evidence (GRADE)
Gifts	Receiving higher number of gifts associated with belief that PSR (pharmaceutical representative) have no impact on their prescribing behaviour[1 14 39]	–	–	–	Moderate
Drug samples	Positive attitude towards the drug industry and the representatives[11 21 34]	Higher prescription of the company drug[21 41]	–	–	High
Pharmaceutical representative speakers	–	Irrational prescribing [16 18 34]	Inability to identify false claims[16]	Increased prescription of sponsor's drug[24]	High
Honoraria and research funding	Positive attitude towards sponsor's drug[60]	–	–	Increased prescription of sponsor's drug[24]	Low
Conference travel	–	Significant increase in prescribing of sponsor drug[18]	–	Increased prescription of sponsor's drug[24]	Low
Industry-paid lunches	Positive attitude towards sponsor's drug[14 34]	Significant increase in prescribing of sponsor drug[62]	–	Increased formulary request for company drug[11 21]	High
CME sponsorship	Positive attitude towards sponsor's drug[24 65]	Avoidance of industry-sponsored CME associated with more rational prescribing habits[33]			Moderate
Interaction withPSR	Positive attitude towards PSR drugs[1 11 14 58]	Higher prescription of the company drug[24]	Positive correlation between the physicians' prescribing cost and the information provided by the drug representative during the interaction[26]	Increased prescription of sponsor's drug[24]	High

However, there was a significant association between attending industry-paid lunches and increased prescription of branded drugs.[52 53 72]

Health care: conflicted, confused, and in need of change

Conflicts of interest in medicine are a serious, pervasive issue. Yet there is insufficient leadership and resolve within global institutions to adequately address this issue. We are concerned with how to ensure transparency of interests and what conflicts of interest should be allowed even if fully disclosed. The second question remains moot while the first remains unsolved, and this is what we discuss here.

In the USA, inconsistent reporting of funding from the pharmaceutical industry to doctors[1] led to the

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CH and MM have written to the UK Health Select Committee urging them to address the conflicts of interest issues in medicine, and are jointly presenting a talk on conflicts of interest at the EvidenceLive Conference in July, 2019. MM is a general practice partner with income from book authorship, freelance writing, and broadcasting and is also senior Fellow in Evidence and Values at the Royal College of General Practitioners and honorary fellow at the Centre for Evidence Based Medicine (CEBM) in Oxford. MM donates money to Keep our NHS Public. MM has received travel and occasional locum payments for giving talks to public, professional, and newspaper groups but never from public relations, pharmaceutical, or technology companies. CH has received expenses and fees for his media work. CH has received expenses from WHO and holds grant funding from the NIHR Oxford BRC and the NIHR School of Primary Care Research Evidence Synthesis Working Group (Project 390). CH has received financial remuneration from an asbestos case. CH receives expenses for teaching EBM and is also paid for his general practice work in the NHS out of hours. CEBM jointly runs the EvidenceLive Conference with the BMJ and the Overdiagnosis Conference with some international partners which are based on a non-profit making model. CH is Editor in Chief of *BMJ Evidence-Based Medicine* and is an NIHR Senior Investigator. SF is a Fellow in Evidence and Values at the Royal College of General Practitioners and a research fellow at the University of Birmingham and receives income from freelance writing, lecturing, and book authorship.

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We should surely aim for a statutory declaration of interests by all professionals and individuals who work in health care internationally, with registers that are publicly accessible, searchable, and permanent. Individuals who have declarations should already be making them, and a streamlined system would be more efficient and stop the current multiple venues of declaration. Employers and regulators that require annual declarations could simply request it through a central register.

House of Commons
Health Committee

The Influence of the Pharmaceutical Industry

Fourth Report of Session 2004–05

Volume I

Report, together with formal minutes

It is extraordinary that there are stricter controls on hospital specialists prescribing than on GPs. We recommend tougher restrictions be placed on what non-specialists can prescribe and greater vigilance to guard against excessive or inappropriate prescribing. Nurse and pharmacist prescribing will need to be carefully monitored. Doctors, in particular 'key opinion leaders', should be obliged to declare significant sums or gifts they receive as hospitality. Professional bodies should maintain a register of these declarations.

Carl Heneghan

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Carl Heneghan is a clinical epidemiologist with expertise in EBM, research methods, evidence synthesis and regulatory science. He has considerable experience in NonCommunicable Diseases and is Director of a World Health Organization Collaboration Centre and expertise in conducting systematic reviews having **Published 91 SRs**, and authored the **Tamiflu systematic reviews**. He is Director of the NIHR SPCR **Evidence Synthesis Working Group** a collaboration of nine primary care departments

His work also includes investigating drug and devices, advising governments on regulatory evidence and working extensively with the public and the media.

He has investigated the evidence for sports drinks, IVF 'Add-on' treatments, metal-hips, screening, surgical mesh, medical devices and hormone pregnancy tests. He has worked in the field of diagnosis for over 15 years and

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Conflicts of interest and payments:

Carl has received expenses and fees for his media work (including payments from BBC Radio 4 Inside Health). He has received expenses from the WHO, FDA, and holds grant funding from the NIHR, the NIHR School of Primary Care Research, The NIHR BRC Oxford and the WHO. He has received financial remuneration from an asbestos case and to date has given legal advice on mesh cases. He has also received income from the publication of a series of toolkit books published by Blackwells. On occasion, he receives expenses for teaching EBM and is also paid for his GP work in NHS out of hours (contract with Oxford Health NHS Foundation Trust). He is Director of CEBM, which jointly runs the **EvidenceLive** Conference with the BMJ and the **Overdiagnosis Conference** with international partners, based on a non-profit making model. He is Editor in Chief of BMJ Evidence-Based Medicine and is an NIHR Senior Investigator.

DPhil Students: Carl welcomes informal contacts from

Sunshine UK

A register of doctors' declared interests.

Are you a doctor?

Make your own self-declarations

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Who we are

Who's behind this site

ABOUT US

What's this all about?

Doctors may receive money and benefits from a wide range of sources. They may be paid by the pharmaceutical industry to give lectures to other doctors. They may run companies that sell health services to the NHS. They may receive hospitality, such as food and drink, or accept free travel and hotel accommodation from industry in order to attend conferences. They may accept free training about which treatments work best, that has been funded by drug companies. They may be paid by industry to conduct research. They may be paid by PR companies working on behalf of drug companies, or providers of health services, such a companies making supplements, health products, or foods.

It can be hard to determine what a 'conflict' is, and of course what is a conflict in one context might not be a conflict in another. This is why we describe this site for 'declarations of interest' as we

Should doctors with commercial interests lead research on their products? Should we forget ‘conflicts’ and discus ‘declarations of interest’ instead? Who should hold and maintain conflicts of interest registers for doctors? Should practicing doctors work with the pharma industry as well as serve on guideline committees? Should researchers with extensive financial interests be disqualified from studies of their own products?

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Thank You