

Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry

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INTERACTIONS BETWEEN PHYSICIANS and the pharmaceutical industry have received increasing amounts of attention over the last several years. Several authors have described significant contact between the pharmaceutical industry and academic researchers,¹ faculty physicians,² community physicians,³ residents,⁴ and medical students.⁵ More importantly, these types of interactions have been shown to influence prescribing patterns,⁶ stimulate requests for addition of drugs to hospital formularies,² result in favorable publications⁷ and research articles,^{8,9} and be related to the lack of publication of unfavorable articles.¹⁰

Clinical practice guidelines (CPGs) are intended to present a synthesis of current evidence and recommendations preformed by expert clinicians and may affect the practice of large numbers of physicians. As a result, any influence that the authors of CPGs experience from their interactions with pharmaceutical companies may be transmitted many times over to the readers of CPGs. Consequently, if individual authors have relationships that pose a potential conflict of interest, readers of these CPGs may wish to know about them to evaluate the merit of those guidelines.

To date, no published data exists regarding the extent to which the au-

Context Increasing contact has been reported between physicians and the pharmaceutical industry, although no data exist in the literature regarding potential financial conflicts of interest for authors of clinical practice guidelines (CPGs). These interactions may be particularly relevant since CPGs are designed to influence the practice of a large number of physicians.

Objective To quantify the extent and nature of interactions between authors of CPGs and the pharmaceutical industry.

Design, Setting, and Participants Cross-sectional survey of 192 authors of 44 CPGs endorsed by North American and European societies on common adult diseases published between 1991 and July 1999. One hundred authors (52%) provided usable responses representing 37 of 44 different CPGs that we identified.

Main Outcome Measures Nature and extent of interactions of authors with drug manufacturers; disclosure of relationships in published guidelines; prior discussion among authors regarding relationships; beliefs regarding whether authors' own relationships or those of their colleagues influenced treatment recommendations in guidelines.

Results Eighty-seven percent of authors had some form of interaction with the pharmaceutical industry. Fifty-eight percent had received financial support to perform research and 38% had served as employees or consultants for a pharmaceutical company. On average, CPG authors interacted with 10.5 different companies. Overall, an average of 81% (95% confidence interval, 70%-92%) of authors per CPG had interactions. Similarly, all of the CPGs for 7 of the 10 diseases included in our study had at least 1 author who had some interaction. Fifty-nine percent had relationships with companies whose drugs were considered in the guideline they authored, and of these authors, 96% had relationships that predated the guideline creation process. Fifty-five percent of respondents indicated that the guideline process with which they were involved had no formal process for declaring these relationships. In published versions of the CPGs, specific declarations regarding the personal financial interactions of individual authors with the pharmaceutical industry were made in only 2 cases. Seven percent thought that their own relationships with the pharmaceutical industry influenced the recommendations and 19% thought that their coauthors' recommendations were influenced by their relationships.

Conclusions Although the response rate for this survey was low, there appears to be considerable interaction between CPG authors and the pharmaceutical industry. Our study highlights the need for appropriate disclosure of financial conflicts of interest for authors of CPGs and a formal process for discussing these conflicts prior to CPG development.

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thors of CPGs interact with the pharmaceutical industry. This study seeks to provide empirical evidence concerning this issue to improve the process of CPG development in the future.

METHODS

Study Questions

We attempted to compare the amount of financial interaction that authors of CPGs had with the pharmaceutical industry with the amount of interaction that was disclosed in the published guidelines that they had authored. We also sought to assess the nature of these interactions and the authors' perceptions of the impact of interactions on recommendations made by the guideline committee. We asked 4 specific questions: (1) How much interaction do authors of clinical practice guidelines have with drug manufacturers and what is the nature of this interaction (ie, do the relationships predate or postdate the guideline writing process)? (2) What physician-pharmaceutical interactions are disclosed in the published guidelines? (3) Prior to beginning the guideline creation process, was there any discussion among the guideline authors regarding relationships with the pharmaceutical industry? and (4) Do guideline authors believe that their relationships or those of their colleagues influence the treatment recommendations that were put forth in the guidelines?

Selection and Review of Articles

Authors were identified by reviewing CPGs endorsed by North American and European societies on common adult diseases published between 1991 and July 1999. The list of medical conditions to be included was created using the 20 most commonly prescribed drugs that are paid for by the Ontario Drug Benefit Program. Drugs that are used symptomatically to treat many potentially nonspecific conditions were excluded (eg, acetaminophen with codeine, lorazepam). If not already included, we added conditions that accounted for the 5 most common admission diagnoses to the internal

medicine services at our hospitals (ie, pneumonia, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease/asthma, and gastrointestinal bleeding). Finally, we excluded diseases for which CPGs did not exist.

Pertinent CPGs were identified through the MEDLINE database, reference lists from published articles, and interviews with expert clinicians. We restricted our sample to CPGs that had been endorsed by a recognized North American or European society and had identifiable authors. We selected the principal authors and, when indicated, those who participated in drafting the guideline to be surveyed.

The CPGs were reviewed and specific declarations of potential financial conflict of interest were recorded. Declarations regarding the guideline creation process and individual authors were classified as no specific declaration made, declaration that no financial interaction existed, declaration that funding was received from a pharmaceutical company, or declaration that funding was received from a nonindustry source (eg, government agency, professional society/association). Statements indicating that the guidelines had been prepared or approved by the endorsing professional association without explicitly indicating from where funds had been received were coded as having no specific declaration made.

Survey Instrument and Data Collection

Two surveys were used in this study. First, a survey instrument based on that of Chren and Landefeld² and used by Stelfox et al⁷ was developed to examine authors' financial interactions with pharmaceutical companies. Manufacturers of drugs used to manage diabetes, chronic obstructive pulmonary disease/asthma, hypertension, pneumonia, coronary artery disease, congestive heart failure, hyperlipidemia, osteoarthritis, depression, and peptic ulcer disease were identified. For each of these manufacturers, authors were asked whether they had any of 6 types of fi-

nancial interactions, including support for attendance at a symposium (eg, funds for travel expenses), honorarium for speaking at a symposium, support for organization of an educational program, support for research, employment by or consultancy for the company, and equity in the company.

The addresses of the corresponding authors were obtained from the articles, a citation index, and other articles published by the same authors. All authors were mailed the survey questionnaire with a cover letter explaining the purpose of the study. Reminder letters and questionnaires were mailed to authors who did not respond to the first mailing within 12 weeks.

Second, respondents to the first survey were resurveyed to characterize the nature of relationships and the disclosure process. Authors were asked whether their relationships specifically involved companies whose drugs were considered or included in the guideline they authored, whether these relationships predated or postdated the guideline process, whether they believed their own relationships or those of their coparticipants influenced the recommendations that were put forward, whether there was discussion among the participants prior to beginning the guideline process regarding any relationships and whether this process was formalized, and how potential conflicts of interest were managed.

Data Analysis

Descriptive statistics were used to examine the results of both quantitative surveys. The results are reported as proportions and means with 95% confidence intervals (CIs). The rate of response to the surveys was similarly analyzed. Analyses were conducted using STATA, version 7 (STATA Corp, College Station, Tex).

RESULTS

One hundred twenty CPGs were identified by our search strategy, of which 35 were excluded because a major North American or European society

Table 1. Type of Relationship With Pharmaceutical Manufacturers and No. of Companies With Which Authors Had Relationships

Relationship	% of Authors (95% Confidence Interval) (n = 100)	Mean No. of Companies (Range) (n = 87)
Any relationship	87 (80-94)	10.5 (1-37)
Travel funding/honorarium	53 (43-63)	5.4 (1-16)
Speaker honorarium	64 (54-74)	7.3 (1-20)
Educational program support	51 (41-61)	4.7 (1-36)
Research support	58 (48-68)	6.7 (1-26)
Employee/consultant	38 (28-48)	5.7 (1-21)
Equity	6 (1-11)	1.8 (1-4)

did not endorse the CPG and 38 were excluded because they were editorials about CPGs or comparisons of different CPGs. Therefore, 47 CPGs were initially included.¹¹⁻⁵⁷ Subsequently, 1 CPG was excluded because the authors could not be identified⁵⁵ and 2 CPGs were excluded after the authors had been surveyed since these were evaluations of CPGs rather than actual CPGs.^{56,57} Therefore, 44 CPGs with 192 authors were included in the study.

Current addresses of 13 authors could not be located and 3 authors had died, resulting in a total of 176 potentially contactable authors. Of these, 107 authors (61%) responded representing 37 of the 44 CPGs included in our study. Therefore, 7 guidelines were not represented in our final sample.^{11,24,32,39,40,42,54} Despite this, all of the disease states that were initially included in our study protocol were still represented by at least 2 CPGs, with the exception of depression, for which there was only 1 CPG included in the sample and for which we received a response. Seven respondents refused to participate, all of whom were involved with different guidelines. Three of these 7 authors were from Europe, 2 were from the United States, and 2 were from Canada. This left 100 completed surveys, which form the basis of our results. Overall, the response rate was 57% of potentially contactable authors and 52% of all authors initially included in our sample. The distribution of sex and disease to which the guidelines pertained was similar for respondents and nonrespondents; however, the distribution of current country of residence was not. Sixty-three

percent of authors currently residing in the United States did not respond whereas 29% of authors living in Canada did not respond ($P = .001$).

Twenty-eight (26%) of 107 authors responded with a letter attached to their survey. These letters could be interpreted as being supportive (21%), neutral (57%), or critical (21%) of our study.

Of the 100 authors who completed the first survey, 1 had died and 1 had moved and was unreachable, leaving 98 potentially contactable authors for the second survey. Of these, 82 (83%) responded. One of these authors refused to participate and 1 could not recall the nature of the disclosure process and, therefore, left the survey blank. Consequently, the response rate for the second survey was 82%.

CPG Author-Pharmaceutical Manufacturer Interactions

The nature of the authors' relationships with pharmaceutical companies is shown in TABLE 1. Eighty-seven percent of the responding authors had some form of interaction with the pharmaceutical industry. Fifty-eight percent had received financial support to perform research and 38% had served as employees or consultants for a pharmaceutical company.

The mean number of companies with which authors who did have financial relationships interacted is shown in Table 1. On average, CPG authors interacted with 10.5 different companies. Authors who received support for research received this funding from a mean of 6.7 companies and those who

served as employees or consultants for pharmaceutical companies did so for a mean of 5.7 companies.

TABLE 2 shows response rates and interactions categorized by the diseases to which the CPGs included in our sample pertained. All of the CPGs for 7 of the 10 disease states had at least 1 author who had some level of interaction. Similarly, the average percentage of authors per CPG who had interactions was 100% for 6 of the 10 disease states. Overall, an average of 81% (95% CI, 70%-92%) of authors per guideline had interactions with the pharmaceutical industry.

Fifty-nine percent of authors had relationships with companies whose products were specifically considered or included in the guideline they authored (TABLE 3). Of these, 96% and 53% had relationships that predated and postdated the guideline process, respectively.

Only 7% believed that their own relationships influenced the treatment recommendations (Table 3). Nineteen percent believed that their coauthors' recommendations were influenced by relationships with the pharmaceutical industry.

Guideline Conflict of Interest Declarations

Forty-five percent of authors reported that prior to beginning the guideline process, discussion occurred among the guideline authors regarding their relationships with the pharmaceutical industry. Of these, 61% reported that there was a formal process for this discussion and 75% indicated that all members of the guideline committee participated.

In the published versions of the 44 CPGs included in the study, authors declared that they had personal financial interactions with the pharmaceutical industry in only 1 guideline⁵¹ (TABLE 4). Similarly, only 1 guideline declared that the authors had no conflicts of interest.¹⁵ In the majority of cases (42 of 44 guidelines), no declarations were made with respect to the authors' potential conflicts of interest.

Table 2. Response Status and Relationship With Pharmaceutical Manufacturers by Disease

Disease	No. of Guidelines Included	No. of Guidelines With at Least 1 Respondent (%)	Authors Responding/ Authors Surveyed (%) [*]	No. of Guidelines in Which at Least 1 Respondent Had Any Interaction (%)	No. of Authors With Any Interaction (%)	Average % of Authors per Guideline With Any Interaction	Mean No. of Companies With Which Authors Had Relationships [†]
Asthma/chronic obstructive pulmonary disease	6	5 (83.3)	6/11 (54.5)	3 (60)	4 (66.7)	60	8.5
Coronary artery disease	6	5 (83.3)	20/37 (54.1)	4 (80)	15 (75)	65	13.1
Heart failure	4	2 (50)	8/16 (50)	2 (100)	7 (87.5)	100	8.3
Depression	1	1 (100)	1/5 (20)	1 (100)	1 (100)	100	11.0
Diabetes	5	4 (80)	9/15 (60)	4 (100)	9 (100)	100	8.0
Peptic ulcer disease	3	3 (100)	3/5 (60)	3 (100)	3 (100)	100	11.7
Hypercholesterolemia	3	3 (100)	9/13 (69.2)	3 (100)	9 (100)	100	10.3
Hypertension	6	5 (83.3)	12/27 (44.4)	4 (80)	10 (83.3)	70	16.9
Osteoarthritis	2	2 (100)	3/87 (37.5)	2 (100)	3 (100)	100	4.0
Pneumonia	8	7 (87.5)	44/70 (62.9)	7 (100)	38 (86.4)	76	9.1

^{*}The total number of authors responding equals 115 (not 100) and the total number of authors surveyed equals 207 (not 192) because several authors participated in more than 1 guideline.

[†]Among authors with relationships.

In 11 of the 44 CPGs, a declaration was made that a pharmaceutical company had sponsored the guideline creation and writing process.^{*} Nonindustry organizations sponsored 9 CPGs.[†] Two of these guidelines were supported by both industry and governmental sources.^{21,27}

COMMENT

Although the results of this study must be interpreted cautiously in light of the relatively low response rate, our results appear to indicate that most CPG authors have interactions with pharmaceutical companies and that a significant proportion work as employees/consultants for drug manufacturers. Moreover, a majority of our respondents indicated that they had relationships with companies whose products were considered in the guideline that they authored, and of these, almost all had relationships that predated the guideline creation process.

The majority of responding authors believed that their relationships had no influence on the recommendations that they put forward. Ideally, we would have liked to have objectively assessed whether this was true by evaluating whether guidelines authored by individuals with relationships recommended use of different therapies than

^{*}References 14, 16, 21-24, 27, 32, 43, 46, 47.

[†]References 15, 17, 18, 21, 27, 30, 40, 41, 51.

Table 3. Nature and Author Perceptions of Relationship With Pharmaceutical Manufacturers

	No. of Authors (%) [95% Confidence Interval]
Had relationship with companies whose drugs were considered in the guideline process	47/80 (59) [48-70]
Relationship predated guideline process	45/47 (96) [92-100]
Relationship postdated guideline process	25/47 (53) [39-67]
Believed that relationships influenced personal recommendations	5/68 (7) [1-9] [*]
Believed that relationships influenced recommendations of colleagues	13/67 (19) [8-30] [†]

^{*}Only 68 of the 80 respondents provided answers to these questions.

[†]Only 67 of the 80 respondents provided answers to these questions.

Table 4. Declarations Contained Within Published Guidelines

Type of Declaration	No. of Guidelines Making Declarations Regarding Authors' Financial Interactions (n = 44)	No. of Guidelines Making Declarations Regarding Guideline Creation Process (n = 44) [*]
No declaration made	42	26
Declared that no sponsorship received	1	0
Received nonpharmaceutical industry support	0	9
Received pharmaceutical industry support	1	11

^{*}Column values total more than 44 because 2 guidelines received funding from both industry and government.

those guidelines authored by individuals without relationships. Unfortunately, most authors had relationships and virtually all guidelines permitted use of a wide range of drugs as first-line agents "if clinically indicated," thereby making any differentiation impossible.

Nevertheless, the authors' perceptions of the influence of their relationships are in stark contrast with the large body of literature that indicates that these types of relationships are indeed significant in other domains.²⁻¹⁰ More-

over, almost 20% of the respondents believed that their colleagues' relationships influenced the recommendations that they put forward.

We wonder whether academicians and physicians underestimate the impact of relationships on their actions because the nature of their professions is the pursuit of objective unbiased information. Unfortunately, bias may occur both consciously and subconsciously, and therefore, its influence may go unrecognized. In fact, pharmaceutical marketing or "detailing" may

rely on the impact of these more subtle forms of influence.⁵⁸ Concern about bias in interpretation of outcomes in randomized trials led to the practice of blinding subjects, their caregivers, and outcome assessors to the knowledge of which treatment the subject received. Is the situation regarding CPG authorship not analogous?

Unlike relationships that individual authors or physicians have with the pharmaceutical industry, financial conflicts of interest for authors of CPGs are of particular importance since they may not only influence the specific practice of these authors but also those of the physicians following the recommendations contained within the guidelines.

There are several possible explanations for our low response rate. First, physicians' interactions with the pharmaceutical industry have received increasing amounts of attention in the medical literature¹⁻¹⁰ and popular press. As a consequence, physicians may have been reluctant to disclose their relationships. Second, the cover letter that we sent to our survey participants made no promise of anonymity. Rather, we indicated that participation in our survey was voluntary. Although we have presented our results in aggregate and never intended to identify individual physicians, it is possible that some authors may have been concerned about being recognized and therefore preferred to not respond. Therefore, based on these factors, it is possible that non-respondents actually had a higher degree of interaction with the pharmaceutical industry than respondents. Consequently, our low response rate may have actually biased our results by underestimating the already high degree of interaction that we observed.

To put our results in perspective without unduly biasing our respondents, we conducted semistructured interviews with 5 guideline authors after the second survey had been completed. These authors underscored the lack of formal process for CPG authors to declare potential conflicts of interest and to sensitize each other to subtle or subconscious influ-

ences, especially for CPGs that were authored more than 5 years ago. In contrast, the interviewees thought that it may be neither possible nor desirable to exclude authors who are involved with industry since the "experts" who write guidelines are the same individuals who are most likely to receive financial support to conduct research. Moreover, our interviewees suggested that an author's objectivity might actually be maintained by having multiple small relationships with different pharmaceutical companies as opposed to large relationships with a few companies. The authors also suggested that relationships with pharmaceutical industries are not the only type of potential conflicts of interest that exist. Concerns regarding obtaining continued funding from governmental agencies (eg, by ensuring that one's government-funded research is included in the studies cited by a CPG) or of individual academic promotion (eg, by ensuring that one's own research is included in the studies cited by a CPG) may also influence the guideline process and may serve as forms of "dual commitment."

Recommendations

Based on our results and the considerable debate that has taken place about the relationships between clinical researchers and the pharmaceutical industry, we propose the following recommendations for the management of potential financial conflicts of interest for authors of clinical practice guidelines.

First, the process whereby authors disclose their potential conflicts of interest must be made more formal. In particular, authors must disclose relationships with the pharmaceutical industry before guideline meetings are held. A full discussion must occur among the participants before the start of the writing process about each person's relationships and how significant relationships (eg, those that predate the guideline process, involve large sums of money, or involve equity positions in companies) will be man-

aged. Participants should be sensitive to the possibility that the influence of these relationships may subconsciously affect their judgments.

Second, authors who have relationships with the pharmaceutical industry need not necessarily be excluded from participating in the guideline creation process. However, authors with significant conflicts of interest should likely be excluded. What level of conflict is significant is clearly a contentious issue. Is there a threshold below which authors will not perceive subconscious influences from their relationships with pharmaceutical companies? The only threshold that is not arbitrary is zero, implying that all authors with any relationships would be excluded. This standard, however, is both impractical and likely too strict. Thus, groups will have to decide on this issue for themselves. However, we do think that authors who hold equity in a company whose products are being considered in the guideline process should be disqualified. This is consistent with the current practices of most governmental granting agencies in North America and the editorial policies of most major medical journals.

Third, there must be complete disclosure to the readers of CPGs of individual authors' financial relationships with the pharmaceutical industry. Ideally, this should occur in the printed version of the guideline. However, if this is not feasible given the large number of authors who may participate in a CPG and practical limitations on space, alternative forms of disclosure, such as the journal's Web site, could be used.

Conclusions

In conclusion, there appears to be a high degree of interaction between authors of clinical practice guidelines and the pharmaceutical industry. These specific interactions may influence the practice of a very large number of physicians. We believe that our study highlights the need for appropriate disclosure of financial conflicts of interest for authors of CPGs and a formal process for discussing these conflicts prior to CPG development.

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