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, faculty physicians, community physicians, residents, and medical students. More importantly, these types of interactions have been shown to influence prescribing patterns, stimulate requests for addition of drugs to hospital formularies, result in favorable publications and research articles, and be related to the lack of publication of unfavorable articles.

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 authors of these CPGs and their colleagues influenced treatment recommendations in guidelines. Authors regarding relationships; beliefs regarding whether authors’ own relationships 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.
authors 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 Landefeld and used by Stelfox et al 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 financial 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

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did not endorse the CPG and 38 were excluded because they were editorial
table or comparisons of different
CPGs. Therefore, 47 CPGs were ini-
tially included. Subsequently, 1 CPG
was excluded because the authors could
not be identified and 2 CPGs were ex-
cluded after the authors had been sur-
veyed since these were evaluations of
CPGs rather than actual CPGs. 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 con-
tactable authors. Of these, 107 authors
(61%) responded representing 37 of the
44 CPGs included in our study. There-
fore, 7 guidelines were not represented
in our final sample. Despite this, all of the disease states that
were initially included in our study pro-
tocol 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 respon-
dents refused to participate, all of whom
were involved with different guide-
lines. 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 ba-
sis of our results. Overall, the response
rate was 57% of potentially contactable
authors and 52% of all authors initially
included in our sample. The distribu-
tion of sex and disease to which the
guidelines pertained was similar for re-
pondents and nonrespondents; how-
ever, the distribution of current coun-
try 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 inter-
preted as being supportive (21%), neu-
tral (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%) re-
responded. One of these authors re-
 fused to participate and 1 could not re-
call the nature of the disclosure process
and, therefore, left the survey blank.
Consequently, the response rate for the
second survey was 82%.

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

CPG Author-Pharmaceutical
Manufacturer Interactions
The nature of the authors’ rela-
tionships with pharmaceutical companies is shown in Table 1. Eighty-seven per-
cent of the responding authors had
some form of interaction with the phar-
maceutical industry. Fifty-eight per-
cent had received financial support to
perform research and 38% had served
as employees or consultants for a phar-
maceutical company.
The mean number of companies with
which authors who did have financial
relationships interacted is shown in
Table 1. On average, CPG authors in-
teracted with 10.5 different compa-
ny. Of these, 61% reported that
there was a formal process for this dis-
cussion and 75% indicated that all
members of the guideline committee
participated.
In the published versions of the 44
CPGs included in the study, authors de-
clared that they had personal financial
interactions with the pharmaceutical indus-
try in only 1 guideline (TABLE 4).
Similarly, only 1 guideline declared that
the authors had no conflicts of inter-
est. In the majority of cases (42 of 44
guidelines), no declarations were made
with respect to the authors’ potential
conflicts of interest.

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 rela-
tionships with the pharmaceutical indus-
try. Of these, 61% reported that
there was a formal process for this dis-
cussion and 75% indicated that all
members of the guideline committee
participated.
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 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 Moreover, 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. 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 literature 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 influences, 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 managed. 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.
REFERENCES