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Interactions between Physicians and Pharmaceutical Industry- Systematic Review

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Abstract

Objectives

The objective of this review is to explore the frequency of physician and pharmaceutical industry interactions, their impact on physicians' attitude, knowledge and behavior

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 were cross sectional studies, cohort studies, randomized trials and survey designs. Studies with narrative reviews, case reports, opinion polls, letters to the editor, systematic reviews and non-English studies 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

PSR interactions influences the physicians' attitudes towards the representatives, their prescribing behavior and increases the number of formulary addition requests for the company's drug. Other interactions such as CME and attending pharmaceutical industry sponsored seminars lead to higher prescribing of the company drug and increasing irrational prescribing behavior.

Conclusion

Physician-PSR interactions and acceptance of gifts and favors from the company's PSRs have been found to affect the physicians' prescribing behavior and contribute to irrational prescription of the company's drug**.** Therefore, intervention in the form of policy implementation and education about the implications of these interactions are needed.

Strengths and limitations of the Study

- Large up-to-date systematic review of studies exploring the effects of physician and pharmaceutical industry representative interactions and their impact on physician attitudes, knowledge and behavior.
- Pubmed, Embase, Cochrane library and Google scholar electronic databases were not searched before 1992 and other databases were not searched.

Introduction

The relationship between physicians and the pharmaceutical industry has evoked heated debate since decades[1]. In 2012, pharmaceutical industry spent $89.5 billion on physician-pharmaceutical sales representative (PSR) interactions, accounting for 60% of the global sales and marketing spending[3-6]. Previous reports have demonstrated that PSRs may influence prescribing behavior[11, 14, 36, 38, 39]. However, the attitudes about PSR interactions are divided and contradictory. Studies have indicated that physicians may be unable to distinguish between promotional information and scientific evidence, while their colleagues more than themselves are susceptible to PSR marketing strategies[22, 27, 32, 34] Most medical and governmental institutions have installed guidelines and self-regulatory and legislative checks to address this controversy[-5,8,9] However, while administration's proposals for deregulatory reforms of Big Pharma are increasing, scientific evidence rigoursly examining this controversy are needed. This review address this question by critically and systemically evaluating the evidence on the impact of PSR interactions on the attitudes of physicians.

Methodology

Inclusion and exclusion criteria:

The following inclusion and exclusion criteria were used to perform this systematic review. (a) Types of studies: Included for data synthesis in this review were cross sectional studies, cohort studies, randomized trials and survey designs that have used analytical methodologies and have focused on at least one facet of extent, impact on behavior and attitude. Excluded were narrative reviews, case reports, opinion polls, letters to the editor, systematic reviews and non-English studies.

(b) Types of participants: Physicians and pharmaceutical representatives.

(c) Types of exposure: Any type of interaction between physicians and the pharmaceutical industry such as meeting with drug representatives, participating in pharmaceutical-sponsored continuing medical education program, and receiving travel funding, free drug samples, industry-provided meals and gifts.

(d) Types of outcome: Knowledge, beliefs, and/or attitudes of physicians regarding physician-industry interactions.

Search strategy:

Pubmed, Embase, Cochrane library and Google scholar electronic databases were searched from 1992 to August 2016 using free text words and medical subject heading relevant to the topic. Databases were not searched before 1992, introducing reporting bias. However, while the relationship between physicians and pharmaceutical representatives is likely to change in time, we did not found studies before 1992 to be reflective of this relationship. Search terms were physician, doctor, healthcare professional, attitude, knowledge, behavior, hospital formulary, professional behavior, prescribing behavior, pharmaceutical representative, interests, marketing strategy, research grant, gifts and meals. Two independent reviewers assessed selected articles as per inclusion/exclusion criteria and shortlisted them for writing the review. Full review protocol is available upon request to the corresponding author.

Results

We independently screened the titles and abstracts of the 2170 identified records for potential eligibility. Out of 2170, full text of 49 eligible citations, which matched the inclusion criteria, were retrieved and used for qualitative assessment during the writing of the review (Figure 1, Table 1).

Characteristics of included studies

The identified studies were published between 1992 and August 2016. Most of the studies included were cross-sectional studies[1, 11-15, 19-23, 26-43, 55, 57, 62, 63, 72, 76]. Only two studies were cohort studies[16, 18], three were randomized trials[17, 25, 74] and one study was a case-control study[24].

Extent of interactions between physicians and the pharmaceutical industry

We found that PSR interactions are a regular feature in the daily lives of physicians across the world [11, 14, 31, 36, 39, 55]. Most of the attending physicians and residents have at least one interaction with the industry representatives per month [14,21, 31, 32, 33]. The frequency of interactions or gifts offered and accepted varies with private versus public hospital setting and the position of the physicians in the medical hierarchy [12, 14, 17, 26, 31, 34, 39, 55, 56]. Medical students are exposed to PSRs from the beginning of their career [34,56]. Junior residents received twice as much free drug samples from PSR interactions than senior residents [14]. PSR interactions were significantly higher at the beginning of residency[39]. The majority of program directors of internal medicine residencies in USA allowed PSRs to meet with residents during working hours and permitted PSR sponsorship of conferences[29]. Attending physicians and physician specialists have greater encounters with PSRs and received more number of medical samples and promotional material than residents[11,31]. Participants working in private practice alone or in both sectors were more likely to receive gifts than doctors working in the public sector [31, 55]. Physicians in academic or hospital-based practice settings had less PSR interactions and significantly lower prescribing costs than physicians in nonacademic and nonhospital practices [26].

Most common gifts received were medical samples[11, 12, 21, 22, 31, 32, 33], promotional material[11, 19, 31] invitations for dinners[11], invitations for CMEs[19, 33], scientific journals[19] and free lunches[22, 32].

Attitude of physicians towards the interactions

We found that physicians have a positive attitude towards PSRs.[1, 12, 13, 17, 23, 27, 29, 33, 39, 43] Physicians perceived PSRs as important sources of education and funding [13, 14, 33, 34, 37, 40]; while some studies reporting skeptical attitudes about contribution of PSRs towards teaching and education [21, 28, 29, 32, 43]. Conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models, and free drug samples were considered as appropriate gifts [17, 23, 28, 57]. Most of the physicians considered pharmaceutical information provided by PSRs, industry sponsored conferences and CME events as important instruments for enhancing their scientific knowledge [13, 33, 37, 40]. Compared to senior residents, significantly more junior residents felt that pharmaceutical representatives have a valuable teaching role [14].

Most of the physicians considered themselves immune to the influence of gifts[1, 13, 14, 15, 20 22, 25, 34]. We found that better scores on knowledge and attitudes were significantly associated with lesser number of interactions with representatives and their gifts[23]. Most studies found that physicians do not believe that PSR interactions impact their prescribing behavoir [1,11, 14, 36, 38, 39, 66, 67], while other studies report found that there was some extent of influence [19, 21, 22, 28, 32, 33, 34] . In addition, physicians considered their colleagues more susceptible than themselves to PSR marketing strategies [1, 22, 27, 32, 34]. There was a strong correlation between the amount of gifts and the belief that PSR interactions did not influence their prescribing behavior [14].

Gifts

Most common gifts received were medical samples[11, 12, 21, 22, 31, 32, 33, 34, 35, 41], promotional material[11, 19, 31, 58] invitations for dinners[11] and scientific journals[19].

Drug samples

Most of the physicians who accepted drug samples had a positive attitude towards the pharmaceutical representatives[11, 12, 21, 22, 31, 32, 33, 34]. Accepting samples lead to higher branded drug prescription rather than generic prescribing [33, 41].

Pharmaceutical representative speakers

Sponsored lectures/symposia of pharmaceutical companies influenced behavior of the attendees, as they prescribed more drugs of the industry without sufficient evidence supporting the drug's superiority [16, 18]. The majority of attending physicians failed to identify inaccurate information about the company drug[59].

Honoraria and Research Funding

Physicians who received money to attend pharmaceutical symposia or conduct research for the company's drug requested formulary addition of that company's drug more often than other physicians[24] (Table 2). Brief encounters with PSRs and receipt of honoraria or research support were predictors of faculty requested change in hospital formulary[60]. Physicians considered company funded clinical trials with skepticism albeit their prescribing behavior was affected favoring the company's drug[61].

Conference travel

Pharmaceutical company sponsored conference travels to touristic locations have quantifiable impact on the prescribing rational of attendees. A significant increase (three times) in the prescribing rate of two company drugs was observed after the physicians attended a company sponsored symposium with all their expenses covered. Despite this significant difference in the prescribing patterns, physicians insisted there was no impact on their prescribing behaviour.[18]

Industry paid lunches

Most physicians received invitations for dinners[11] and free lunches [14, 20, 32, 34]. Clerks, interns and junior residents attended more company sponsored lunches than senior residents [14]. Pharmaceuticals also sponsored departmental lunches during journal clubs[28]. There was no significant association between attending industry paid lunches[22] and dinners[11] and formulary request for that company's drug (Table 2). However, there was a significant association between attending industry paid lunches and increased prescription of branded drugs [62, 63, 64].

CME sponsorship

Physicians who attended company sponsored CME events had more positive attitudes towards and inclination to prescribe the branded drugs [19, 34, 58, 61, 65]. We found that physicians who refused CME sponsorship were seen to prescribe higher proportion of generics and lower expenditure medicines when compared to physicians who attended CMEs[34].

Discussion

We report that there is widespread interaction between the pharmaceutical industry and physicians[11, 14, 31, 36, 39, 55]. Interactions are in the form of personal communications, free gifts such as drug samples, sponsored meals, sponsored conference travel, funding for research and CMEs and honoraria[11, 12, 21, 22, 31, 32, 33]. The frequency of these interactions is comparable between residents and physicians[14, 21, 31, 32, 33]. However, the amount and type of gifts vary with the position of the physician in medical hierarchy, specialization and location of practice[12, 14, 17, 26, 31, 34, 39, 55, 56]. In general, trainees (residents, interns) are treated with more drug samples, stationery items and free meals than senior physicians[14, 39]. Senior physicians usually avail of sponsored conferences/ trips, research funding, honoraria and CME events. The extent of these interactions varies with academic versus non-academic institutions: non-academic hospitals record more interactions than others[12, 26, 31, 55, 76]. The majority of the physicians do not believe that they are affected by PSR interactions [1, 13, 14, 15, 20 22, 25, 34]. However, a sizeable percentage in various surveys responded in the affirmative when asked whether they thought that their peers are vulnerable[1, 22, 27, 32, 34].

We observe that there is a positive correlation between acceptance of gifts and physicians' urge to reciprocate favorably towards the benefactor[33, 38, 41]. More the amount and monetary value of the interactions, Considering that physicians have a social contract with society at large to provide unbiased and altruistic service, this is an alarming observation. Countries have put into effect legislation and policies to curb activities that abuse the role of physicians as gatekeepers of society's health, which are discussed below.

Policies and educational intervention

The relationship of physicians with patients is of fiduciary nature. Hence activities that might affect that relationship by altering physicians' clinical behavior are not acceptable. Physician-PSR interactions may put the trust of patients in physicians at risk. Interaction with PSRs

begins at medical school. Trainees are exposed to PSR marketing and promotional techniques from the initial years of their medical education, which impact their prescribing behavior in future. Overall, trainees, i.e., residents and interns, are more vulnerable to PSR interactions than senior physicians[30,36,56]. Physicians are susceptible to PSR interactions, which influences their clinical decision-making leading to greater prescriptions of branded drugs over low cost generic medicines and increasing healthcare cost [33, 41, 62, 63, 64]. In addition, this is accompanied by requests to add the benefactor company's drug to existing hospital formulary[24].. Therefore, there is need to institute and implement stringent policies curtailing physician-PSR relationships, as well as educational programs to increase awareness among medical students in their formative years. Previous reports have indicated that implementing policies and conducting educational programs are effective in increasing awareness of physician's attitudes towards PSR interactions[25,51,71, 72, 73, 74]. .

Limitiations of the study

Pubmed, Embase, Cochrane library and Google scholar electronic databases were not searched before 1992 and other databases were not searched.

Future implications

PSR interactions compromise the objectivity of the physicians and results in irrational prescribing behavior and increasing healthcare cost Educating physicians and increasing regulation of PSR interactions may lower the likelihood of prescribing new non-superior industry drugs and irrational prescription behavior. Further studies are required to evaluate the benefits of various intervention based education programs on the clinical and ethical behavior of the physicians.

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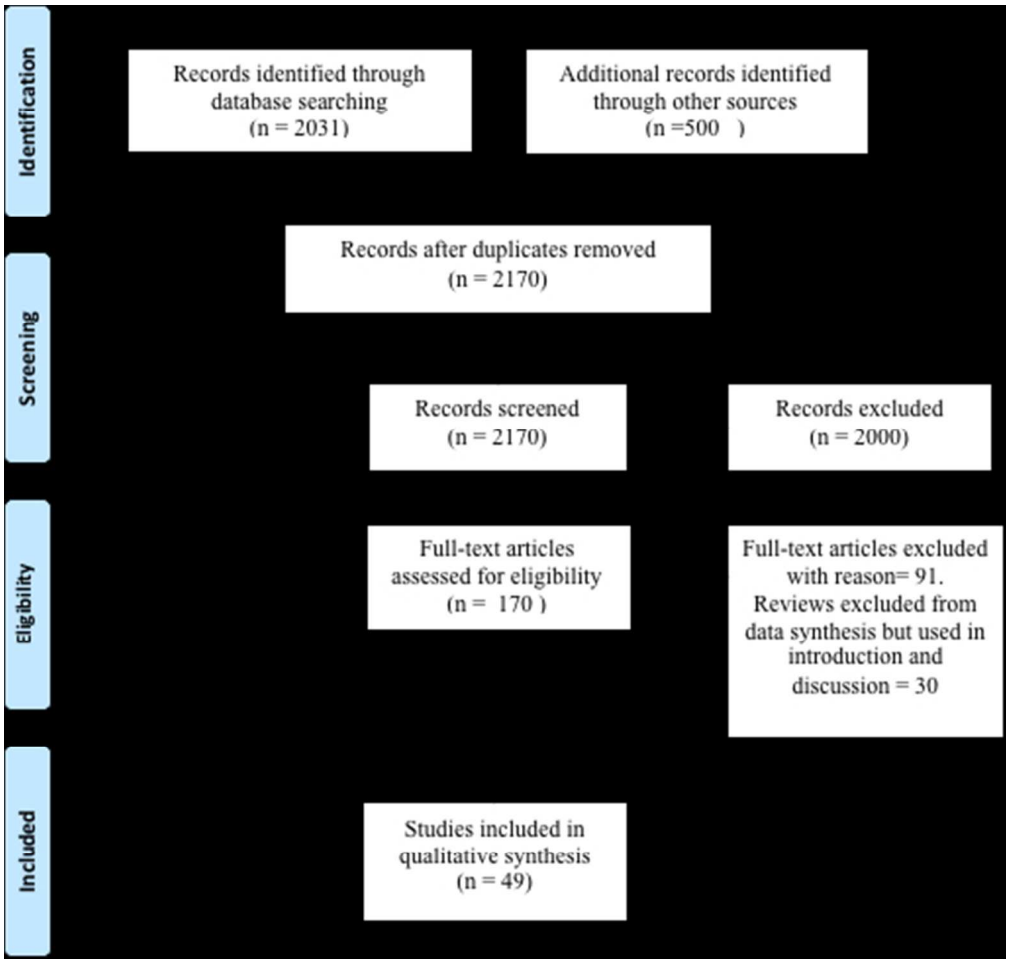
Legends

Figure 1: PRISMA flow diagram showing search strategy and included studies

Table 1: Characteristics of included studies

Table 2: Impact of physician-pharmaceutical industry interaction on physician



PRISMA flow diagram showing search strategy and included studies

180x171mm (72 x 72 DPI)

Study	Authors	Study sample	Study design	Interaction	Summary
1	Steinman et al., 2001	Residents	Cross-sectional	Interaction with representative, drug samples	Impact on prescribing
11	De Ferrari et al., 2014	Physicians	Cross-sectional	Interaction, medical samples, promotional material, dinners	Positive attitude towards representatives
12	Thomson et al., 1994	Physicians	Cross-sectional	Interaction with representative, drug samples	Positive attitude towards industry
13	Kamal et al., 2015	Physicians	Cross-sectional	Interaction with representative	Positive attitude towards industry
14	Hodges, 1995	Residents of psychiatry	Cross-sectional	Interaction with representative	Positive attitude towards gifts
15	Gibbons et al., 1998	Physicians and residents	Cross-sectional	Gifts, samples, travel, lunches	Positive attitude towards gifts
16	Spingarn et al., 1996	Internal medicine residents	Cohort	Teaching	Negative effect on prescribing
17	Zaki, 2014	Physicians	Randomized, cross-sectional survey	Conferences, drug samples	Favorable towards promotion
18	Orlowski et al., 1994	Physicians	Cohort	Conference travel	Negative effect on prescribing
19	Scheffer et al., 2014	Physicians prescribing antiretroviral drugs	Cross-sectional	Interaction with representative, drug samples, journals	Frequency of interaction
20	Brett et al., 2003	Physicians	Cross-sectional	Interaction with representative	Impact on attitudes
21	Gupta et al., 2016	Doctors	Cross-sectional	Interaction with representative, drug samples, journals	Impact on prescribing
22	Morgan et al., 2006	Obstetrician-gynaecologists	Cross-sectional	Drug samples, lunch	Impact on prescribing, positive attitudes
23	Alosaimi et al., 2014	Physicians	Cross-sectional	Interaction with	Positive attitude

				representative	towards industry
24	Chren et al., 1994	Faculty physicians	Case control	Honoraria, research	Requested formulary additions of drug
25	Randall et al., 2005	Residents	Controlled trial	Interaction with representative	Impact on prescribing and attitudes
26	Caudil et al., 1996	Physicians	Cross-sectional	Interaction with representative	Negative impact on prescribing patterns
27	Andaleeb et al., 1995	Physicians	Cross-sectional	Interaction with representative	Positive attitude towards industry
28	Reeder et al., 1993	Residents of emergency medicine	Cross-sectional	Interaction with representative	Believed that no impact on their prescribing
29	Lichstein et al., 1992	Directors, internal medicine	Cross-sectional	Interaction with representative	Positive attitude towards industry
30	Brotzman et al., 1992	Directors, residency programs	Cross-sectional	Interaction with representative	No guidelines for interaction with representatives
31	Alssageer et al., 2012	Doctors	Cross-sectional	Interaction with representative, drug samples, printed materials	Positive attitude towards industry
32	Lieb & Brandtonies, 2010	Physicians	Cross-sectional	Interaction with representative, drug samples, printed materials, lunches	Frequency and impact on attitudes
33	Lieb & Scheurich, 2014	Physicians	Cross-sectional	Interaction with representative, drug samples, printed materials, CME	High expenditure prescribing
34	Lieb & Koch, 2013	Medical students	Cross-sectional	Interaction with representative, drug samples, printed	Positive attitude towards industry, impact on their

				materials, lunches	prescribing
35	Brown et al., 2015	Directors, residency programs	Cross-sectional	Interaction with representative, gifts, lunches	Negative attitude towards industry
37	Rahmana et al., 2015	Doctors	Cross-sectional	Interaction with representative	Impact on their prescribing
38	Lee & Begley, 2016	Physicians	Cross-sectional	Gifts	Negative impact on their prescribing
39	Montastruc et al., 2014	Medical residents	Cross-sectional	Interaction with representative	Negative attitude towards industry Believed that no impact on their prescribing
40	Ketis & Kersnik, 2013	Family physicians	Cross-sectional	Interaction with representative	Positive effect on knowledge
41	Hurley et al., 2014	Dermatologists	Cross-sectional	Free drug samples	Impact on their prescribing (less generic prescribing)
42	Makowska, 2014	Doctors	Cross-sectional	Gifts	Positive attitude towards industry
43	Siddiqui et al., 2014	Medical students	Cross-sectional	Interaction with representative	Positive attitude towards industry
55	Workneh BD et al., 2016	Physicians	Cross-sectional	Interaction with representative, gifts	Positive attitude towards industry, impact on prescribing behavior
57	Khan N et al., 2016	Doctors	Cross-sectional	Interaction with representative, gifts	Positive attitude towards industry
58	Saito S et al. 2010	Physicians	National Survey	Interaction with industry, receipt of gifts, funds, CME, samples	Positive attitude towards representatives and gifts, value information from representatives,

					interactions higher with physicians who prefer to prescribe brand names.
59	Ziegler MG et al. 1995	Pharmaceutical representative speakers	Survey	Accuracy of information provided by PSRs about drugs	Incorrect information often provided by speakers goes unnoticed by physicians
60	Lurie N et al., 1990	Internal medicine house staff and faculty	Survey	Effect of conversation with PSRs, free meals, honoraria and research support	Impact on prescribing behavior and formuary change requests.
62	DeJong C et al., 2016	Physicians	Cross-sectional	Industry sponsored meals	Receipt of industry-sponsored meals was associated with an increased rate of brand name prescription.
63	Yeh JS et al., 2016	Physicians	Cross-sectional	Effect of industry payment on prescription of branded drugs for cholesterol control	Payment for meals and educational programs increased prescription of brand names.
65	Bowman MA et al., 1988	Physician attendees	Self report survey	Effect of CME on prescribing behavior	Sponsoring company's drugs were favored during prescription
66	Fischer MA et al., 2009	Physicians, trainees	Survey of focused groups	Effect of industry marketing strategies on prescription and cognitive dissonance of physicians	Believed that no impact on their prescribing, have ability to evaluate information of PSRs
67	Chimonas S et al., 2007	Physicians	Survey of focused groups	Determine how physicians handle their cognitive	Physicians understood the conflict of interests but developed

				dissonance	denials and rationalizations to deal with cognitive dissonance.
72	Yeh JS et al., 2014	Medical students	Cross-sectional	Interaction with representative, gifts, lunches	Policies separating students from representatives reduced number of interactions
73	Larkin I et al., 2014	Pediatricians, child & adolescent psychitrist	Survey	Interaction with representative	Anti detailing policies reduced the prescription of off-label antidepressants and anti psychotics for children
74	Esmaily HM et al., 2010	General physicians	Randomized trial	Effect of outcome based CME	Outcome based CME reduced total number of prescriptions, prescriptions of antibiotics, anti-inflammatories and injections compared to traditional CME. It also improved compliance to regulations.
76	Parikh K et al., 2016	Pediatricians	Cross-sectional	Comparison of industry interactions between pediatricians and other specialists; among subspecialities of pediatrics.	Pediatricians get fewer gifts from industry than internists. There is variation among sub specialities for extent of interaction.
78	Chressanthis GA et al. 2012	Physicians	Survey	Effect of restricting PSRs on clinical practice and knowledge	Restricting PSRs affected information flow about drugs, both negative and positive.

#	Attitudes	Prescribing behavior	Knowledge	Formulary requests
Gifts	Receiving higher number of gifts was associated with belief that PRs have no impact on their prescribing behaviour ($p<0.05$)[14]	-	-	-
Drug samples	Positive attitude towards the drug industry and the representatives[11, 12, 21, 22, 31, 32, 33, 34]	Higher prescription of the company drug[21, 33, 41]	-	-
Pharmaceutical representative speakers	-	Rational treatment (OR, 8.4; 95% CI, 2.1-38.9) Irrational treatment ($p= 0.03$ [16]) [16, 18, 34]	Inability to identify the false claims[16, 59]	Request for sponsor's drug vs physicians who did not benefit (OR, 3.9; 95% CI, 1.2-12.7)[24]
Honoraria and Research Funding	Positive attitude towards sponsor's drug ($p<0.05$ [19])[19, 60, 61]	-	-	Request for sponsor's drug vs physicians who did not benefit (OR, 3.9; 95% CI, 1.2-12.7)[24]
Conference travel	-	Significant increase in prescribing of sponsor drug (about 3 times higher than before attending) ($p<0.001$)[18]	-	Request for sponsor's drug vs physicians who did not benefit (OR, 3.9; 95% CI, 1.2-12.7)[24]
Industry paid lunches	Positive attitude towards sponsor's drug ($p<0.05$)[19, 14, 20, 32, 34]	Significant increase in prescribing of sponsor drug [62, 63, 64]	-	There was no significant association between attending the industry paid lunches[21] and dinners[11] and formulary request for that company drug
CME sponsorship	Positive attitude towards sponsor's drug ($p<0.05$ [19]) [19, 34, 58, 61, 65]	High expenditure prescribing[34]		

Interaction with PR	Interaction with PR was associated with positive attitude towards PR (p= 0.02) Positive attitude towards the gifts, travel, samples, etc (r = 0.706; p = 0.02)[30]	Higher prescription of the company drug[21]	A significant positive correlation was found between the physicians' prescribing cost and the information provided by the drug representative during the interaction (P < 0.01)[26]	Interaction with PR resulted in increased request for PR's drug vs physicians who had no interactions with PR (OR, 3.4; 95% CI, 1.8-6.6)[24]

OR-Odds ratio, PR-Pharmaceutical representative, CI-Confidence interval

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3/4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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Association between pharmaceutical sales representatives' interaction on physicians' attitudes and prescribing habits: A systematic review

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Association between pharmaceutical sales representatives' interaction on physicians' attitudes and prescribing habits: A systematic review

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All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

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Data sharing statement: any data relevant to a published article will be made available alongside the article when published.

Abstract

Objectives

The objective of this review is to explore the frequency of physician and pharmaceutical industry interactions, their impact on physicians' attitude, knowledge and behavior.

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 were cross sectional studies, cohort studies, randomized trials and survey designs. Studies with narrative reviews, case reports, opinion polls, letters to the editor, systematic reviews and non-English studies 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 sales representative (PSR) interactions influences the physicians' attitudes towards the representatives, their prescribing behavior and increases the number of formulary addition requests for the company's drug. Other interactions such as continuing medical education (CME) and attending pharmaceutical industry sponsored seminars lead to higher prescribing of the company drug and increasing irrational prescribing behavior.

Conclusion

Physician-pharmaceutical sales representatives interactions and acceptance of gifts and favors from the company's pharmaceutical sales representatives have been found to affect the physicians' prescribing behavior and are likely to contribute to irrational prescription of the company's drug**.** Therefore, intervention in the form of policy implementation and education about the implications of these interactions are needed.

Strengths and limitations of the study

- Large up-to-date systematic review of studies exploring the effects of physician and pharmaceutical industry representative interactions and their impact on physician attitudes, knowledge and behavior.
- This systematic review used the recommendations outlined in the Cochrane Handbook for conducting systematic reviews and the 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

Keywords: pharmaceutical sales representative; physicians, drug industry; brand prescriptions; conflict of interest ;physicians-industry interactions; pharmaceutical industry; attitude of health personnel; gifts to physicians; medical education; irrational prescriptions

Introduction

The relationship between physicians and the pharmaceutical industry has evoked heated debate for many decades [1]. In 2012, the pharmaceutical industry spent $89.5 billion on physician-pharmaceutical sales representative (PSR) interactions, accounting for 60% of the global sales and marketing spending [2-8]. Previous reports have demonstrated that PSRs may influence prescribing behavior [9-16]. However, the attitudes about PSR interactions are divided and contradictory. Studies have indicated that physicians may be unable to distinguish between promotional information and scientific evidence [17, 18]. Physicians on the other hand believe their colleagues are more susceptible to PSR marketing strategies than themselves [19-22]. Most medical and governmental institutions have installed guidelines and self-regulatory and legislative checks to address this controversy [5, 15, 16, 23-26]. However, while administrative proposals for deregulatory reforms of the pharmaceutical industry are increasing, scientific evidence rigorously examining this controversy are needed. This review addresses this question by critically and systemically evaluating the evidence on the impact of PSR interactions on the attitudes of physicians.

Methodology

Protocol

We followed a detailed methodology that we described in our review protocol, which is available upon request to the corresponding author. Two independent reviewers assessed selected articles as per inclusion/exclusion criteria as per standardization in the protocol, shortlisted them for writing the review and cross-checked each other. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1).

Eligibility criteria

The eligibility criteria were:

- Types of studies: cross sectional studies, cohort studies, randomized trials and survey designs comparing an intervention of interest to a comparator on at least one facet of extent, impact on behavior and attitude. Excluded were narrative reviews, case reports, opinion polls, letters to the editor and systematic reviews.
- Types of participants: physicians, pharmaceutical representatives, physicians in training/residents. We did not consider medical students or other health professionals.

- Types of exposure: any type of interaction between physicians and the pharmaceutical industry where there is direct interaction with the physician, such as meeting with drug representatives, participating in pharmaceutical-sponsored CME event, receiving travel funding, free drug samples, industry-provided meals, gifts to the individual and active presentation of industry-related information to the physician.
- Types of outcome: knowledge of physicians (e.g. accuracy of knowledge related to a specific medication), beliefs and/or attitudes of physicians regarding physician-industry interactions (e.g. perceived influence of information from the pharmaceutical company on their behavior), behavior of physicians (e.g. prescribing quantity/frequency).Type of control: either not interaction or a lower level of interaction.
- Exclusion criteria were: qualitative, ecological, econometric studies, editorials, letters to the editor, studies on medical students, small samples sizes, studies assessing non-targeted or indirect interactions (e.g. journal advertisement) and research funding.

We did not exclude studies based on risk of bias. We took risk of bias into account when grading the quality of evidence using GRADE approach.

Search strategy

The search strategy included Pubmed, Embase, Cochrane library and Google scholar electronic databases (January 1992 to August 2016). Databases were not searched before 1992, as these studies were already investigated in an earlier review [27]. The search combined terms for physicians and pharmaceutical, and included both free text words and medical subject heading relevant to the topic. We did not use a search filter. The supplementary information file provides the full details of the search strategies. Additional search strategies included a search of the grey literature (theses and dissertations). Also, we reviewed the references lists of included and relevant papers [27-29].

Assessment of risk of bias in included studies

Two reviewers assessed in duplicate and independently the risk of bias in each eligible study. They resolved disagreements by discussion or with the help of a third reviewer. We used the recommendations outlined in the Cochrane Handbook to assess the risk of bias in randomized

studies. We graded each potential source of bias and rated the studies as high, low or unclear risk of bias.

Data analysis and synthesis

We assessed the agreement between reviewers for full-text screening by calculating the kappa statistic. We did not conduct a meta-analysis due to the heterogeneity of study design, types of interventions, outcomes assessed, and outcome measures used. Instead, we summarized the data narratively. We assessed the quality of evidence by outcome using the GRADE methodology [30].

Results

We independently screened the titles and abstracts of the 2170 identified records for potential eligibility. Out of 2170, full text of 49 eligible citations, which matched the inclusion criteria, were retrieved and used for qualitative assessment during the writing of the review (Figure 1, Table 1). We excluded 2000 records as they were not relevant (n = 1641), not original research (n=269), about medical students (n=4) and non-medical (e.g. ecological, econometric; n=86).

Characteristics of included studies

The identified studies were published between 1992 and August 2016. Most of the studies included were cross-sectional studies [1, 9-13, 19, 21, 22, 31-55]. Only two studies were cohort studies [56, 57], three were randomized trials [58-60] and one study was a case-control study [61].

Extent of interactions between physicians and the pharmaceutical industry

We found that PSR interactions are a regular feature in the daily lives of physicians across the world [9-11, 13, 42, 50]. Most of the attending physicians and residents have at least one interaction with the industry representatives per month [10, 21, 22, 36, 42]. The frequency of interactions or gifts offered and accepted varies with private versus public hospital setting and the position of the physicians in the medical hierarchy [10, 13, 31, 38, 42, 43, 50, 58, 62]. Junior residents received twice as much free drug samples from PSR interactions than senior residents [10]. PSR interactions were significantly higher at the beginning of residency [13]. The majority of program directors of internal medicine residencies in USA allowed PSRs to meet with residents during working hours and permitted PSR sponsorship of conferences [40]. Attending physicians and physician specialists have greater encounters with PSRs and received more

numbers of medical samples and promotional material than residents [9, 42]. Participants working in private practice alone or in both sectors were more likely to receive gifts than physicians working in the public sector [42, 50]. Physicians in academic or hospital-based practice settings had less PSR interactions and significantly lower prescribing costs than physicians in nonacademic and nonhospital practices [38]. Most common gifts received were medical samples [9, 21, 22, 31, 36, 37, 42, 63], promotional material [9, 34, 42] invitations for dinners [9], invitations for CMEs [22, 34], scientific journals [34] and free lunches [21, 37].

Attitude of physicians towards the interactions

We found that physicians have a positive attitude towards PSRs [1, 13, 19, 20, 22, 31, 32, 40, 49, 58, 64]. Physicians perceived PSRs as important sources of education and funding [10, 22, 32, 43, 45, 46], while some studies reporting skeptical attitudes about contribution of PSRs towards teaching and education [21, 36, 39, 40, 49]. Conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models, and free drug samples were considered as appropriate gifts [19, 39, 51, 58]. Most of the physicians considered pharmaceutical information provided by PSRs, industry sponsored conferences and CME events as important instruments for enhancing their scientific knowledge [22, 32, 45, 46]. Compared to senior residents, significantly more junior residents felt that pharmaceutical representatives have a valuable teaching role [10]. Most of the physicians considered themselves immune to the influence of gifts [1, 10, 32, 33, 35, 37, 43, 59]. We found that better scores on knowledge and attitudes were significantly associated with lesser number of interactions with representatives and their gifts [19]. Most studies found that physicians do not believe that PSR interactions impact their prescribing behavoir [1, 9-13, 65, 66], while other studies found that there was some extent of influence [21, 22, 34, 36, 37, 39, 43]. In addition, physicians considered their colleagues more susceptible than themselves to PSR marketing strategies [1, 20, 21, 37, 43]. There was a strong correlation between the amount of gifts and the belief that PSR interactions did not influence their prescribing behavior [10].

Gifts

Most common gifts received were medical samples [9, 21, 22, 31, 36, 37, 42-44, 47], promotional material [9, 34, 42, 67] invitations for dinners [9] and scientific journals [34].

Drug samples

Most of the physicians who accepted drug samples had a positive attitude towards the pharmaceutical representatives [9, 21, 22, 31, 36, 37, 42, 43]. Accepting samples lead to higher branded drug prescription rather than generic prescribing [22, 47].

Pharmaceutical representative speakers

Sponsored lectures/symposia of pharmaceutical companies influenced behavior of the attendees leading to the attendees prescribing more drugs from the sponsoring companies without sufficient evidence supporting superiority of those drugs [56, 57]. The majority of attending physicians failed to identify inaccurate information about the company drug [18]. This might make them more prone to interactions of pharmaceutical sales representatives to prescribe in favor of the company drug.

Honoraria and Research Funding

Physicians who received money to attend pharmaceutical symposia or to perform research requested formulary addition of the company's drug more often than other physicians, This association was independent of many confounding factors [61] (Table 2). Brief encounters with PSRs and receipt of honoraria or research support were predictors of faculty requested change in hospital formulary [68].

Conference travel

Pharmaceutical company sponsored conference travels to touristic locations have quantifiable impact on the prescribing rational of attendees. A significant increase (three times) in the prescribing rate of two company drugs was observed after the physicians attended a company sponsored symposium with all their expenses covered. Despite this significant difference in the prescribing patterns, physicians insisted there was no impact on their prescribing behaviour [57].

Industry paid lunches

Most physicians received invitations for dinners [9] and free lunches [10, 21, 35, 43]. Clerks, interns and junior residents attended more company sponsored lunches than senior residents [10]. Pharmaceutical companies also sponsored departmental lunches during journal clubs [39]. There was no significant association between attending industry paid lunches [37] and dinners [9] and formulary request for that company's drug (Table 2). However, there was a significant

association between attending industry paid lunches and increased prescription of branded drugs [52, 53, 69].

CME sponsorship

Physicians who attended company sponsored CME events had more positive attitudes towards and inclination to prescribe the branded drugs [28, 34, 43, 67, 70]. We found that physicians who refused CME sponsorship were seen to prescribe higher proportion of generics and lower expenditure medicines when compared to physicians who attended CMEs [22].

Discussion

We report that there is widespread interaction between the pharmaceutical industry and physicians [9-11, 13, 42, 50]. Interactions are in the form of personal communications, free gifts such as drug samples, sponsored meals, sponsored conference travel, funding for research and CMEs and honoraria [9, 21, 22, 31, 36, 42]. The frequency of these interactions is comparable between residents and physicians [10, 21, 22, 36, 42]. However, the amount and type of gifts vary with the position of the physician in medical hierarchy, specialization and location of practice [10, 13, 31, 38, 42, 43, 50, 58, 62]. In general, trainees (residents, interns) are treated with more drug samples, stationery items and free meals than senior physicians [10, 13]. Senior physicians usually avail of sponsored conferences/ trips, research funding, honoraria and CME events. The extent of these interactions varies with academic versus non-academic institutions: non-academic hospitals record more interactions than others [31, 38, 42, 50, 55]. The majority of the physicians do not believe that they are affected by PSR interactions [1, 10, 32, 33, 35, 37, 43, 59]. However, a sizeable percentage in various surveys responded in the affirmative when asked whether they thought that their peers are vulnerable [1, 20, 21, 37, 43]. It is further noted that there is a trend towards non-physician clinicians interactions and prescribing, such as nurses whom, also, generally hold a positive attitude toward PSR-interactions. This further depicts the extent of interactions and also might expose a risk of replicating irrational prescribing in non-physicians [71].

We observe that there is a positive correlation between acceptance of gifts and physicians' urge to reciprocate favorably towards the benefactor [12, 22, 47]. Considering that physicians have a social contract with society at large to provide unbiased and altruistic service and also the impact of these interactions on healthcare costs, this is an alarming observation. Countries have put into effect legislation and policies to curb activities that abuse the role of physicians

as gatekeepers of society's health, such as the The Sunshine Act which is the first Congressional involvement in regulating the disclosure by physicians of payments by pharmaceutical companies and manufacturers of drugs, federal health care programmes are required to report certain payments and items of value given to physicians and teaching hospitals (e.g. speaking fees, consulting arrangements, and free food) [72-74]. The purpose is to prevent undue influence and protect the public interest. Moreover, a 2005 joint report by the WHO and Health Action International (HAI) reported on interventions to counter promotional activities [75]. The evidence presented in that report was not eligible for our systematic review, mostly because it related to interventions on students or doctors-in-training. Nevertheless, the findings suggested that interventions such as industry self-regulation and guidelines for sales representatives are not effective, while education about drug promotion might influence physician attitudes [76-78].

Policies and educational intervention

The relationship of physicians with patients is of a fiduciary nature. Hence activities that might affect that relationship by altering physicians' clinical behavior are not acceptable. Physician-PSR interactions may put the trust of patients in physicians at risk. Interaction with PSRs begins at medical school. Trainees are exposed to PSR marketing and promotional techniques from the initial years of their medical education, which impact their prescribing behavior in future. Overall, trainees, i.e., residents and interns, are more vulnerable to PSR interactions than senior physicians [11, 41, 62]. Physicians are susceptible to PSR interactions, which influences their clinical decision-making leading to greater prescriptions of branded drugs over low cost generic medicines and increasing healthcare costs [22, 47, 52, 53, 69]. In addition, this is accompanied by requests to add the benefactor company's drug to existing hospital formulary [61]. Therefore, there is need to institute and implement stringent policies curtailing physician-PSR relationships, as well as educational programs to increase awareness. Previous reports have indicated that implementing policies and conducting educational programs are effective in increasing awareness of physician's attitudes towards PSR interactions [54, 59, 60, 76, 79-83].

Strengths and Limitations of the study

A major strength of this study is that is a large up-to-date systematic review of studies exploring the effects of physician and pharmaceutical industry representative interactions and their impact on attitudes, knowledge and prescribing behavior of practicing physicians and

residents in different settings (e.g. academic, primary care). Another strength of this study is the use of Cochrane and GRADE methodologies for conducting a review and assessing the quality of the studies. Moreover, we performed an extensive search in 3 databases and the grey literature. Some of the limitations of this review are related to the included studies, as some did not provide evidence for the significance of their findings or had varying study designs and outcomes, which made it impossible to conduct a meta-analysis. Also, the included studies were subject to risk of bias related to the lack of validity of outcome measurement, and inadequate handling of significant potential confounders. Another limitation is that our search was limited from January 1992 to August 2016.

Future implications

PSR interactions compromise the objectivity of the physicians and are likely to result in irrational prescribing behavior and increasing healthcare costs. Educating physicians and increasing regulation of PSR interactions may lower the likelihood of prescribing new non-superior industry drugs and irrational prescription behavior. Further studies are required to evaluate the benefits of various intervention based education programs on the clinical and ethical behavior of the physicians.

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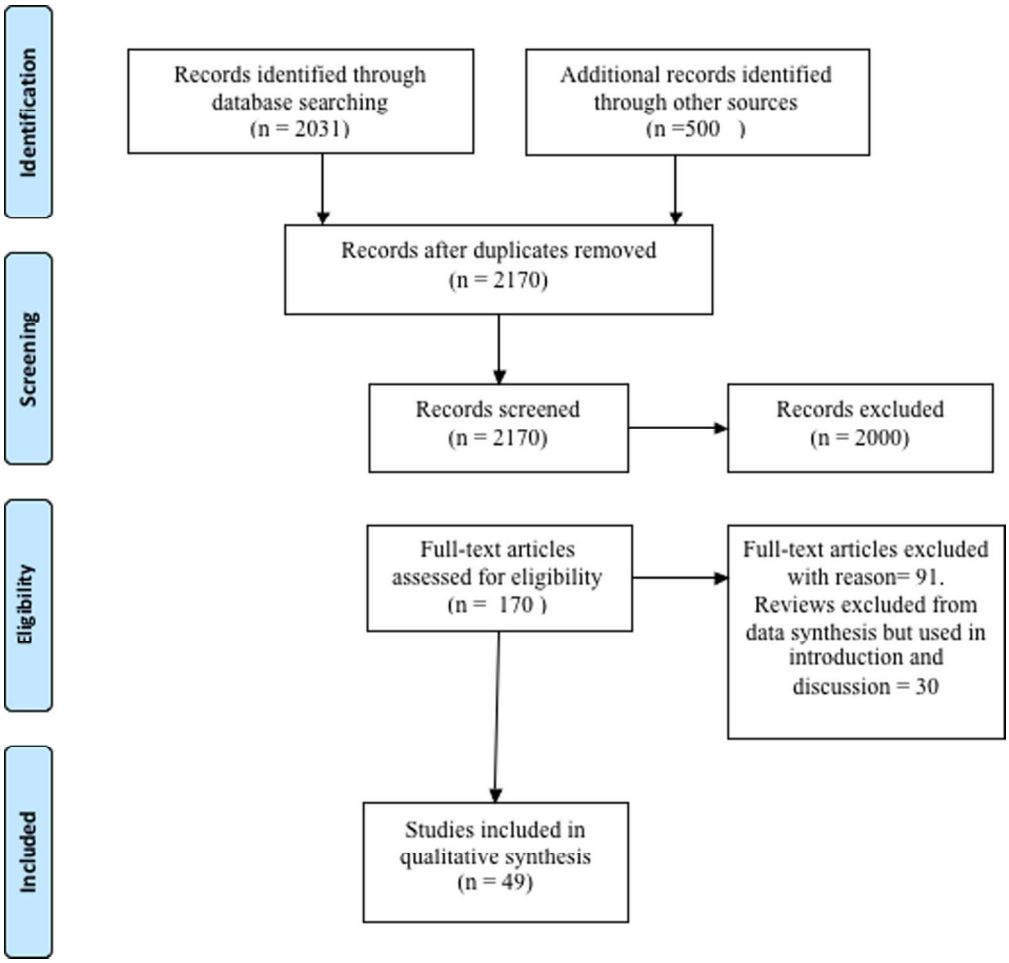

Flow diagram of study selection.

Study	Authors	Country	Participants, setting	Study design	Interaction	Outcomes
1	Steinman et al., 2001	USA	Surveys about attitudes and behaviors toward industry gifts in 105 residents at a university-based internal medicine residency program	Cross-sectional	PSR interactions, gifts	Most participants (61%) hold positive attitudes toward gifts from industry and PSR interactions and believe they do not influence their own prescribing, but only 16% believed other physicians were similarly unaffected (P< .0001)
11	De Ferrari et al., 2014	Peru	Questionnaire in 155 faculty and trainee physicians of five different clinical departments working in a public general hospital	Cross-sectional	PSR interactions, medical samples, promotional material, dinners	Positive attitude towards representatives (88.5% of participants). Faculty physicians received a larger amount of medical samples and promotional material and were more prone to believe that gifts and lunches do not influence their prescribing behavior (42.2% vs. 23.6%; p=0.036)
12	Thomson et	New	Questionnaire	Cross-	Interactions with	Most general

	al., 1994	Zealand	survey of 67 general practitioners	sectional	PSR	practitioners (67%) had a negative attitude toward PSR interaction
13	Kamal et al., 2015	Egypt	Interviews with 18 physicians	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
14	Hodges, 1995	Canada	Survey in 105 residents of psychiatry	Cross-sectional	Interaction with PSR, drug samples, lunches	Positive attitude towards PSR interaction (56.5% of participants). The more money and promotional items a participant had received, the more likely he or she was to believe that discussions with representatives did not affect prescribing ($p < 0.05$)
15	Gibbons et al., 1998	USA	Survey of 392 physicians in two tertiary-care medical centers	Cross-sectional	PSR interactions,gifts, samples, travel, lunches	Positive attitude towards PSR interactions, gifts, samples and lunches
16	Spingarn et al., 1996	USA	75 internal medicine physicians in university medical center	Retrospective cohort	PSR interaction (teaching)	Attendees inappropriately prescribed PSR speakers drug compared to non-attendees ($p=0.029$)
17	Zaki, 2014	Saudi Arabia	Survey of 250 physicians	Randomized, cross-sectional survey	Conferences, drug samples	Favorable towards promotion
18	Orlowski et	USA	10 physicians that	Cohort	Conference	Significant

	al., 1994		were invited for a symposium and tracking the pharmacy inventory usage reports for these drugs before and after the symposia		travel	increase in the prescribing pattern of drugs occurred following the symposia (p<0.001)
19	Scheffer et al., 2014	Brazil	Survey of 300 physicians prescribing antiretroviral drugs	Cross-sectional	Interaction with representative, drug samples, journals	Frequency of interaction; the majority of (64%) of the physicians had multiple forms of interactions with PSR
20	Brett et al., 2003	USA	Questionnaire of 93 physicians in a medical school	Cross-sectional	Interaction with PSR	Impact on attitudes; most physicians believed that most of PSR activities do not pose major ethical problems
21	Gupta et al., 2016	India	Survey of 81 physicians in single hospital	Cross-sectional	Interaction with representative, drug samples, journals	Impact on prescribing; 61.7% of participants think that PSR has an impact on their prescribing (P = 0.0001)
22	Morgan et al., 2006	USA	Survey of 397 obstetrician-gynaecologists	Cross-sectional	Drug samples, promotional material, lunch	Impact on prescribing, positive attitudes; most respondents thought it's proper to accept drug samples (92%), lunch (77%), an anatomical model (75%) or a well-

						paid consultantship (53%) from PSR
23	Alosaimi et al., 2014	Saudi Arabia	Survey of 659 physicians	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
24	Chren et al., 1994	USA	40 case physicians and 80 control physicians	Case control	PSR interactions, honoraria, research	Increased prescription of company's drug after PSR interaction, honoraria and research ($p<0.001$, all)
25	Randall et al., 2005	USA	Intervention group of physicians (n=18) that received education about PSR interaction and control group (n=14)	Controlled trial	Interaction with PSR	The majority of residents found the interactions and gifts useful. Compared to the comparison group, the intervention group significantly decreased the reported number of office supplies and noneducational gifts ($p<0.05$)
26	Caudil et al., 1996	USA	Survey of 446 primary care physicians	Cross-sectional	Interaction with PSR	Significant positive correlation between physician cost of prescribing and perceived credibility, availability, applicability, and use of information

						provided by PSR ($p < 0.01$)
27	Andaleeb et al., 1995	USA	223 physicians in northwestern Pennsylvania	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
28	Reeder et al., 1993	USA	87 residents of emergency medicine	Cross-sectional	Interaction with PSR, gifts	Most participants believed that PSR interaction had no impact on their prescribing
29	Lichstein et al., 1992	USA	272 directors of internal medicine residency programs	Cross-sectional	Interaction with PSR	Most participants had a positive attitude towards PSR interactions
30	Brotzman et al., 1992	USA	Directors of 386 family practice residency programs	Cross-sectional	Interaction with PSR	Majority of programs do not have guidelines for interaction with PSR
31	Alssageer et al., 2012	Libya	Survey of 608 physicians in public and private practice settings	Cross-sectional	Interaction with PSR, drug samples, printed materials	Positive attitude towards PSR interactions
32	Lieb & Brandtonies, 2010	Germany	Survey of 208 physicians (neurology, cardiology and general medicine)	Cross-sectional	Interaction with PSR, drug samples, printed materials, lunches	Frequency and impact on attitudes
33	Lieb & Scheurich, 2014	Germany	Survey of 160 physicians in private and public practices	Cross-sectional	Interaction with representative, drug samples, printed materials, CME	High expenditure prescribing; avoidance of industry-sponsored CME is associated with more rational prescribing habits
34	Lieb & Koch, 2013	Germany	Survey of 1038 medical students at 8 universities	Cross-sectional	Interaction with representative, drug samples,	Most participants have contact

					printed materials, lunches	with the pharmaceutical company; 24.6% of the participants thought gifts would influence their future prescribing behavior, while 45.1% thought gifts would influence their classmates' future prescribing behavior (p<0.001)
35	Brown et al., 2015	USA	251 directors of family medicine residency programs	Cross-sectional	Interaction with PSR, gifts, lunches	Negative attitude towards PSR interactions
37	Rahmana et al., 2015	Bangladesh	Survey of 83 village physicians	Cross-sectional	Interaction with PSR	Impact on their prescribing
38	Lee & Begley, 2016	USA	Nationally representative survey of 4720 physicians	Cross-sectional	Gifts	Gifts were associated with lower perceived quality of patient care; an inverse relationship between the frequency of received gifts and the perceived quality of care was observed
39	Montastruc et al., 2014	France	Survey among 631 medical residents	Cross-sectional	Interaction with representative	Most participants believed that PSR interaction had no impact on their prescribing; participants

						who had a more positive opinion were more frequently exposed to PSR (p<0.001)
40	Ketis & Kersnik, 2013	Slovenia	895 family physicians at the primary level of care	Cross-sectional	Interaction with PSR	Positive effect on knowledge; Participants value PSRs' selling and communication skills and trustworthiness highly
41	Hurley et al., 2014	USA	3500 dermatologists	Cross-sectional	Free drug samples	Impact on their prescribing; the provision of samples with a prescription by dermatologists has been increasing over time, and this increase is correlated (r = 0.92) with the use of the branded generic drugs promoted by these sample
42	Makowska, 2014	Poland	Survey of 382 physicians	Cross-sectional	Gifts	Positive attitude towards PSR interactions
43	Siddiqui et al., 2014	Pakistan	Questionnaires of 352 medical students	Cross-sectional	Interaction with representative	Positive attitude towards PSR interaction
55	Workneh BD et al., 2016	Ethiopia	Survey of 90 physicians from public and private health facilities	Cross-sectional	Interaction with representative, gifts	Positive attitude towards industry, impact on

						prescribing behavior; Nearly half of the physicians reported that their prescribing decisions were influenced by PSR
57	Khan N et al., 2016	Pakistan	Questionnaires in 472 physicians	Cross-sectional	Interaction with representative, gifts	Positive attitude towards PSR interaction
58	Saito S et al. 2010	Japan	1417 physicians working in internal medicine, general surgery, orthopedic surgery, pediatrics, obstetrics-gynecology, psychiatry, and ophthalmology	National Survey	Interaction with industry, receipt of gifts, funds, CME, samples	Positive attitude towards PSR and gifts, value information from PSR, interactions higher with physicians who prefer to prescribe brand names
59	Ziegler MG et al. 1995	USA	27 physicians working in public and private hospitals	Survey	Accuracy of information provided by PSRs about drugs	Incorrect information often provided by speakers goes unnoticed by physicians
60	Lurie N et al., 1990	USA	240 internal medicine faculty physicians in academic medical centers	Survey	Effect of interaction with PSR, free meals, honoraria and research support	Impact on prescribing behavior and formulary change requests
62	DeJong C et al., 2016	USA	279.669 physicians who wrote Medicare prescriptions in any of 4 drug classes: statins, cardioselective β-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor	Cross-sectional	Industry sponsored meals	Receipt of industry-sponsored meals was associated with an increased rate of brand name prescription.

			blockers (ACE inhibitors and ARBs), and selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs) Physicians			
63	Yeh JS et al., 2016	USA	All licensed Massachusetts physicians who wrote prescriptions for statins paid for under the Medicare drug benefit in 2011 (n=2444)	Cross-sectional	Effect of industry payment on prescription of branded drugs for cholesterol control	Payment for meals and educational programs increased prescription of brand name statins.
65	Bowman MA et al., 1988	USA	121 physician attendees	Self report survey	Effect of CME on prescribing behavior	Sponsoring company's drugs were favored during prescription
66	Fischer MA et al., 2009	USA	Multi-disciplinary focus groups with 61 physicians	Survey	Effect of industry marketing strategies on prescription and cognitive dissonance of physicians	Most participants reported no PSR impact on their prescribing, value to have ability to evaluate information of PSRs
67	Chimonas S et al., 2007	USA	Six focus groups in 32 academic and community physicians	Survey	PSR interactions	Positive attitude towards PSR interaction
72	Yeh JS et al., 2014	USA	1610 US medical students	Cross-sectional	Interaction with representative, gifts, lunches	Policies separating students from representatives reduced number of interactions
73	Larkin I et al., 2014	USA	Pediatricians, child & adolescent psychiatrists in five medical centers	Survey	Interaction with PSR	Anti detailing policies reduced the prescription of off-label antidepressants and anti

						psychotics for children
74	Esmaily HM et al., 2010	Iran	112 general physicians were randomized in two groups: 1) outcome-based educational intervention for rational prescribing and 2) concurrent CME program in the field of rational prescribing	Randomized trial	Effect of outcome and retinal prescribing	Rational prescribing improved in some of the important outcome-based indicators. No difference between two arms of the study
76	Parikh K et al., 2016	USA	descriptive, cross-sectional analysis of Open Payments data and 9 638 825 payments to physicians and pediatricians from January 1 to December 31, 2014	Cross-sectional	Comparison of PSR interactions between pediatricians and other specialists; among subspecialities of pediatrics.	Pediatricians get fewer gifts from PSR than internists. There is variation among sub specialities for extent of interaction.
78	Chressanthis GA et al. 2012	USA	Clinical decisions of 72,114 physicians were statistically analyzed using prescription data	Survey	Effect of restricting PSRs on clinical practice and knowledge	Restricting PSRs affected information flow about drugs, both negative and positive.

#	Attitudes	Prescribing behavior	Knowledge	Formulary requests	Quality of Evidence (GRADE)
Gifts	Receiving higher number of gifts associated with belief that PRs have no impact on their prescribing behaviour [1,10,13]	-	-	-	**Moderate**
Drug samples	Positive attitude towards the drug industry and the representatives [9,36,43]	Higher prescription of the company drug [36, 47]	-	-	**High**
Pharmaceutical representative speakers	-	Irrational prescribing [56, 57, 43]	Inability to identify false claims[56]	Increased prescription of sponsor's drug[61]	**High**
Honoraria and Research Funding	Positive attitude towards sponsor's drug [68]	-	-	Increased prescription of sponsor's drug[61]	**Low**
Conference travel	-	Significant increase in prescribing of sponsor drug[57]	-	Increased prescription of sponsor's drug[61]	**Low**
Industry paid lunches	Positive attitude towards sponsor's drug [10, 43]	Significant increase in prescribing of sponsor drug[52]	-	Increased formulary request for company drug [9,36]	**High**
CME sponsorship	Positive attitude towards sponsor's drug [61, 70]	Avoidance of industry-sponsored CME associated with more rational prescribing habits [22]			**Moderate**

Interaction with PRS	Positive attitude towards PSR drugs [1,9,10,67]	Higher prescription of the company drug[61]	Positive correlation between the physicians' prescribing cost and the information provided by the drug representative during the interaction[38]	Increased prescription of sponsor's drug[61]	**High**

Search strategy for PubMed search engine of Medline

In an attempt to find all related literature on the topic, studies related to physician-pharmaceutical representative interactions that affect the prescribing behavior of the physicians were identified through computerized searches using, but not limited to, the following subject headings and text words in PubMed from 1992 to 2016.

1. Physician interactions with pharmaceutical industry
2. Physician attitude towards pharmaceutical representatives
3. Behavior of physicians towards pharmaceutical representatives
4. Gifts AND physician AND pharmaceutical representatives
5. Honoraria AND physician AND pharmaceutical representatives
6. Continuing medical education AND physician AND pharmaceutical representatives
7. Research funding AND physician AND pharmaceutical representatives
8. Conference travel AND physician AND pharmaceutical representatives
9. Industry sponsored meals AND physician behavior

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3/4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Association between pharmaceutical sales representatives' interaction on physicians' attitudes and prescribing habits: A systematic review

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Association between pharmaceutical sales representatives' interaction on physicians' attitudes and prescribing habits: A systematic review

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All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

Contributor Statement: All authors have contributed equally and have substantial contributions to the conception or design of the work; Author Freek Fickweiler for the acquisition, analysis, and interpretation of data for the work; Author Freek Fickweiler for drafting the work and Authors Ewout Urbach and Ward Fickweiler for revising it critically for important intellectual content; and all authors (Freek Fickweiler, Ward Fickweiler and Ewout Urbach) contributed to final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interest: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

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Data sharing statement: any data relevant to a published article will be made available alongside the article when published.

Abstract

Objectives

The objective of this review is to explore the frequency of physician and pharmaceutical industry interactions andits impact on physicians' attitude, knowledge and behavior.

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, randomized trials and survey designs. Studies with narrative reviews, case reports, opinion polls, letters to the editor, systematic reviews and non-English studies 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 sales representative (PSR) interactions influences the physicians' attitudes towards the representatives, their prescribing behavior and increases the number of formulary addition requests for the company's drug.

Conclusion

Physician-pharmaceutical sales representatives interactions and acceptance of gifts and favors from the company's pharmaceutical sales representatives have been found to affect the physicians' prescribing behavior and are likely to contribute to irrational prescription of the company's drug**.** Therefore, intervention in the form of policy implementation and education about the implications of these interactions are needed.

Strengths and limitations of the 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 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

Keywords: pharmaceutical sales representative; physicians, drug industry; brand prescriptions; conflict of interest ;physicians-industry interactions; pharmaceutical industry; attitude of health personnel; gifts to physicians; medical education; irrational prescriptions

Introduction

The relationship between physicians and the pharmaceutical industry has evoked heated debate for many decades[1]. In 2012, the pharmaceutical industry spent $89.5 billion on physician-pharmaceutical sales representative (PSR) interactions whichaccounted for 60% of the global sales and marketing spending[2-8]. Previous reports have demonstrated that PSRs may influence prescribing behavior[9-16]. However, the evidence determining whether or not PSR interactions influence physicians are divided and contradictory. Studies have indicated that physicians may be unable to distinguish between promotional information and scientific evidence[17-18]. Physicians on the other hand believe their colleagues are more susceptible to PSR marketing strategies than themselves [19-22]. The majority of the physicians do not believe that they are affected by PSR interactions. Most medical and governmental institutions have installed guidelines and self-regulatory and legislative checks to address this controversy[5,15,16, 23-26]. However, while administrative proposals for deregulatory reforms that would remove some governmental authority over the industry are increasing, scientific evidence rigorously examining this controversy are needed. This review addresses this controversy by critically and systemically evaluating the evidence on the impact of PSR interactions on physicians.

Methodology

Protocol

We followed a detailed methodology that we described in our review protocol, which is available upon request to the corresponding author. Two independent reviewers assessed selected articles as per inclusion/exclusion criteria, shortlisted them for writing the review and cross-checked each other. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1).

Eligibility criteria

The eligibility criteria were:

- Types of studies: cross sectional studies, cohort studies, randomized trials and survey designs comparing an intervention of interest on at least one facet of extent, impact on behavior and attitude.
- Types of participants: physicians, pharmaceutical representatives, physicians in training/residents. We did not consider medical students or other health professionals.

- Types of exposure: any type of interaction between physicians and the pharmaceutical industry where there is direct interaction with the physician, such as meeting with drug representatives, participating in pharmaceutical-sponsored CME event, receiving travel funding, free drug samples, industry-provided meals, gifts to the individual and active presentation of industry-related information to the physician
- Types of outcome: knowledge of physicians (e.g. accuracy of knowledge related to a specific medication), beliefs and/or attitudes of physicians regarding physician-industry interactions (e.g. perceived influence of information from the pharmaceutical company on their behavior), behavior of physicians (e.g. prescribing quantity/frequency)
- Type of control: no interaction.
- Exclusion criteria were: qualitative, ecological, econometric studies, editorials, letters to the editor, studies on medical students, small samples sizes, studies assessing non-targeted or indirect interactions (e.g. journal advertisement) and research funding.

We did not exclude studies based on risk of bias. We took risk of bias into account when grading the quality of evidence using GRADE approach.

Search strategy

The search strategy included Pubmed, Embase, Cochrane library and Google scholar electronic databases (January 1992 to August 2016). Databases were not searched before 1992, as these studies were already investigated in an earlier review[27]. The search combined terms for physicians and pharmaceutical, and included both free text words and medical subject heading relevant to the topic. We did not use a search filter. The supplementary information file provides the full details for one database. Additional search strategies included a search of the grey literature (theses and dissertations). Also, we reviewed the references lists of included and relevant papers.[27-29]

Assessment of risk of bias in included studies

Two reviewers assessed in duplicate and independently the risk of bias in each eligible study.Disagreements were resolved by discussion or adjudication by a third reviewer. . We used the recommendations outlined in the Cochrane Handbook to assess the risk of bias in randomized studies. We graded each potential source of bias and rated the studies as high, low or unclear risk of bias.

Data analysis and synthesis

The information extracted from the selected studies included type of study, study design, type of PSR interaction and type of outcome. We did not conduct a meta-analysis due to the heterogeneity of study design, types of interventions, outcomes assessed, and outcome measures used. Instead, we summarized the data narratively. We assessed the quality of evidence by outcome using the GRADE methodology[30].

Results

We independently screened the titles and abstracts of the 2170 identified records for potential eligibility. Out of 2170, the full text of 49 eligible citations which matched the inclusion criteria were retrieved and used for qualitative assessment during the writing of the review (Figure 1, Table 1)

Study	Authors	Country	Participants, setting	Study design	Interaction	Outcomes
1	Steinman et al., 2001	USA	Surveys about attitudes and behaviors toward industry gifts in 105 residents at a university-based internal medicine residency program	Cross-sectional	PSR interactions, gifts	Most participants (61%) hold positive attitudes toward gifts from industry and PSR interactions and believe they do not influence their own prescribing, but only 16% believed other physicians were similarly unaffected (P< .0001)
11	De Ferrari et al., 2014	Peru	Questionnaire in 155 faculty and trainee physicians of five different clinical departments working in a public	Cross-sectional	PSR interactions, medical samples, promotional material, dinners	Positive attitude towards representatives (88.5% of participants).

			general hospital			Faculty physicians received a larger amount of medical samples and promotional material and were more prone to believe that gifts and lunches do not influence their prescribing behavior (42.2% vs. 23.6%; p=0.036)
12	Thomson et al., 1994	New Zealand	Questionnaire survey of 67 general practitioners	Cross-sectional	Interactions with PSR	Most general practitioners (67%) had a negative attitude toward PSR interaction
13	Kamal et al., 2015	Egypt	Interviews with 18 physicians	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
14	Hodges, 1995	Canada	Survey in 105 residents of psychiatry	Cross-sectional	Interaction with PSR, drug samples, lunches	Positive attitude towards PSR interaction (56.5% of participants). The more money and promotional items a participant had received, the more likely he or she was to believe that discussions with representatives did not affect prescribing

						($p < 0.05$)
15	Gibbons et al., 1998	USA	Survey of 392 physicians in two tertiary-care medical centers	Cross-sectional	PSR interactions,gifts, samples, travel, lunches	Positive attitude towards PSR interactions, gifts, samples and lunches
16	Spingarn et al., 1996	USA	75 internal medicine physicians in university medical center	Retrospective cohort	PSR interaction (teaching)	Attendees inappropriately prescribed PSR speakers drug compared to non-attendees ($p=0.029$)
17	Zaki, 2014	Saudi Arabia	Survey of 250 physicians	Randomized, cross-sectional survey	Conferences, drug samples	Favorable towards promotion
18	Orlowski et al., 1994	USA	10 physicians that were invited for a symposium and tracking the pharmacy inventory usage reports for these drugs before and after the symposia	Cohort	Conference travel	Significant increase in the prescribing pattern of drugs occurred following the symposia ($p<0.001$)
19	Scheffer et al., 2014	Brazil	Survey of 300 physicians prescribing antiretroviral drugs	Cross-sectional	Interaction with representative, drug samples, journals	Frequency of interaction; the majority of (64%) of the physicians had multiple forms of interactions with PSR
20	Brett et al., 2003	USA	Questionnaire of 93 physicians in a medical school	Cross-sectional	Interaction with PSR	Impact on attitudes; most physicians believed that most of PSR activities do not pose major ethical problems
21	Gupta et al., 2016	India	Survey of 81 physicians in single hospital	Cross-sectional	Interaction with representative, drug samples,	Impact on prescribing; 61.7% of

					journals	participants think that PSR has an impact on their prescribing (P = 0.0001)
22	Morgan et al., 2006	USA	Survey of 397 obstetrician-gynaecologists	Cross-sectional	Drug samples, promotional material, lunch	Impact on prescribing, positive attitudes; most respondents thought it's proper to accept drug samples (92%), lunch (77%), an anatomical model (75%) or a well-paid consultantship (53%) from PSR
23	Alosaimi et al., 2014	Saudi Arabia	Survey of 659 physicians	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
24	Chren et al., 1994	USA	40 case physicians and 80 control physicians	Case control	PSR interactions, honoraria, research	Increased prescription of company's drug after PSR interaction, honoraria and research (p<0.001, all)
25	Randall et al., 2005	USA	Intervention group of physicians (n=18) that received education about PSR interaction and control group (n=14)	Controlled trial	Interaction with PSR	The majority of residents found the interactions and gifts useful. Compared to the comparison group, the intervention group significantly

						decreased the reported number of office supplies and noneducation al gifts ($p<0.05$)
26	Caudil et al., 1996	USA	Survey of 446 primary care physicians	Cross-sectional	Interaction with PSR	Significant positive correlation between physician cost of prescribing and perceived credibility, availability, applicability, and use of information provided by PSR ($p < 0.01$)
27	Andaleeb et al., 1995	USA	223 physicians in northwestern Pennsylvania	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
28	Reeder et al., 1993	USA	87 residents of emergency medicine	Cross-sectional	Interaction with PSR, gifts	Most participants believed that PSR interaction had no impact on their prescribing
29	Lichstein et al., 1992	USA	272 directors of internal medicine residency programs	Cross-sectional	Interaction with PSR	Most participants had a positive attitude towards PSR interactions
30	Brotzman et al., 1992	USA	Directors of 386 family practice residency programs	Cross-sectional	Interaction with PSR	Majority of programs do not have guidelines for interaction with PSR
31	Alssageer et al., 2012	Libya	Survey of 608 physicians in public	Cross-sectional	Interaction with PSR, drug	Positive attitude

			and private practice settings		samples, printed materials	towards PSR interactions
32	Lieb & Brandtonies, 2010	Germany	Survey of 208 physicians (neurology, cardiology and general medicine)	Cross-sectional	Interaction with PSR, drug samples, printed materials, lunches	Frequency and impact on attitudes
33	Lieb & Scheurich, 2014	Germany	Survey of 160 physicians in private and public practices	Cross-sectional	Interaction with representative, drug samples, printed materials, CME	High expenditure prescribing; avoidance of industry-sponsored CME is associated with more rational prescribing habits
34	Lieb & Koch, 2013	Germany	Survey of 1038 medical students at 8 universities	Cross-sectional	Interaction with representative, drug samples, printed materials, lunches	Most participants have contact with the pharmaceutical company; 24.6% of the participants thought gifts would influence their future prescribing behavior, while 45.1% thought gifts would influence their classmates' future prescribing behavior ($p<0.001$)
35	Brown et al., 2015	USA	251 directors of family medicine residency programs	Cross-sectional	Interaction with PSR, gifts, lunches	Negative attitude towards PSR interactions
37	Rahmana et al., 2015	Bangladesh	Survey of 83 village physicians	Cross-sectional	Interaction with PSR	Impact on their prescribing
38	Lee & Begley, 2016	USA	Nationally representative survey of 4720 physicians	Cross-sectional	Gifts	Gifts were associated with lower perceived

						quality of patient care; an inverse relationship between the frequency of received gifts and the perceived quality of care was observed
39	Montastruc et al., 2014	France	Survey among 631 medical residents	Cross-sectional	Interaction with representative	Most participants believed that PSR interaction had no impact on their prescribing; participants who had a more positive opinion were more frequently exposed to PSR ($p<0.001$)
40	Ketis & Kersnik, 2013	Slovenia	895 family physicians at the primary level of care	Cross-sectional	Interaction with PSR	Positive effect on knowledge; Participants value PSRs' selling and communication skills and trustworthiness highly
41	Hurley et al., 2014	USA	3500 dermatologists	Cross-sectional	Free drug samples	Impact on their prescribing; the provision of samples with a prescription by dermatologists has been increasing over time, and this

						increase is correlated (r = 0.92) with the use of the branded generic drugs promoted by these sample
42	Makowska, 2014	Poland	Survey of 382 physicians	Cross-sectional	Gifts	Positive attitude towards PSR interactions
43	Siddiqui et al., 2014	Pakistan	Questionnaires of 352 medical students	Cross-sectional	Interaction with representative	Positive attitude towards PSR interaction
55	Workneh BD et al., 2016	Ethiopia	Survey of 90 physicians from public and private health facilities	Cross-sectional	Interaction with representative, gifts	Positive attitude towards industry, impact on prescribing behavior; Nearly half of the physicians reported that their prescribing decisions were influenced by PSR
57	Khan N et al., 2016	Pakistan	Questionnaires in 472 physicians	Cross-sectional	Interaction with representative, gifts	Positive attitude towards PSR interaction
58	Saito S et al. 2010	Japan	1417 physicians working in internal medicine, general surgery, orthopedic surgery, pediatrics, obstetrics-gynecology, psychiatry, and ophthalmology	National Survey	Interaction with industry, receipt of gifts, funds, CME, samples	Positive attitude towards PSR and gifts, value information from PSR, interactions higher with physicians who prefer to prescribe brand names
59	Ziegler MG et al. 1995	USA	27 physicians working in public and private hospitals	Survey	Accuracy of information provided by	Incorrect information often

					PSRs about drugs	provided by speakers goes unnoticed by physicians
60	Lurie N et al., 1990	USA	240 internal medicine faculty physicians in academic medical centers	Survey	Effect of interaction with PSR, free meals, honoraria and research support	Impact on prescribing behavior and formulary change requests
62	DeJong C et al., 2016	USA	279.669 physicians who wrote Medicare prescriptions in any of 4 drug classes: statins, cardioselective β-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ACE inhibitors and ARBs), and selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs) Physicians	Cross-sectional	Industry sponsored meals	Receipt of industry-sponsored meals was associated with an increased rate of brand name prescription.
63	Yeh JS et al., 2016	USA	All licensed Massachusetts physicians who wrote prescriptions for statins paid for under the Medicare drug benefit in 2011 (n=2444)	Cross-sectional	Effect of industry payment on prescription of branded drugs for cholesterol control	Payment for meals and educational programs increased prescription of brand name statins.
65	Bowman MA et al., 1988	USA	121 physician attendees	Self report survey	Effect of CME on prescribing behavior	Sponsoring company's drugs were favored during prescription
66	Fischer MA et al., 2009	USA	Multi-disciplinary focus groups with 61 physicians	Survey	Effect of industry marketing strategies on prescription and cognitive dissonance of physicians	Most participants reported no PSR impact on their prescribing, value to have ability to evaluate

						information of PSRs
67	Chimonas S et al., 2007	USA	Six focus groups in 32 academic and community physicians	Survey	PSR interactions	Positive attitude towards PSR interaction
72	Yeh JS et al., 2014	USA	1610 US medical students	Cross-sectional	Interaction with representative, gifts, lunches	Policies separating students from representatives reduced number of interactions
73	Larkin I et al., 2014	USA	Pediatricians, child & adolescent psychiatrists in five medical centers	Survey	Interaction with PSR	Anti detailing policies reduced the prescription of off-label antidepressants and anti psychotics for children
74	Esmaily HM et al., 2010	Iran	112 general physicians were randomized in two groups: 1) outcome-based educational intervention for rational prescribing and 2) concurrent CME program in the field of rational prescribing	Randomized trial	Effect of outcome and retinal prescribing	Rational prescribing improved in some of the important outcome-based indicators. No difference between two arms of the study
76	Parikh K et al., 2016	USA	descriptive, cross-sectional analysis of Open Payments data and 9 638 825 payments to physicians and pediatricians from January 1 to December 31, 2014	Cross-sectional	Comparison of PSR interactions between pediatricians and other specialists; among subspecialities of pediatrics.	Pediatricians get fewer gifts from PSR than internists. There is variation among sub specialities for extent of interaction.
78	Chressanthis GA et al. 2012	USA	Clinical decisions of 72,114 physicians were statistically analyzed using prescription data	Survey	Effect of restricting PSRs on clinical practice and knowledge	Restricting PSRs affected information flow about drugs, both

						negative and positive.

. We excluded 2000 records as they were not relevant (n = 1641), not original research (n=269), about medical students (n=4) and non-medical (e.g. ecological, econometric; n=86).

Characteristics of included studies

The identified studies were published between 1992 and August 2016. Most of the studies included were cross-sectional studies[1,9-13,19,21,22,31-55]. Only two studies were cohort studies[56, 57], three were randomized trials[58-60] and one study was a case-control study[61].

Extent of interactions between physicians and the pharmaceutical industry

We found that PSR interactions are a regular feature in the daily lives of physicians across the world [9-11,13,42,50]. Most of the attending physicians and residents have at least one interaction with industry representatives per month [10,21,22,36,42]. The frequency of interactions or gifts offered and accepted varies with private versus public hospital setting and the position of the physicians in the medical hierarchy [10,13,31,38,42,43,50,58,62]. Junior residents received twice as much free drug samples from PSR interactions than senior residents [10]. PSR interactions were significantly higher at the beginning of residency[13]. The majority of program directors of internal medicine residencies in the USA allowed PSRs to meet with residents during working hours and permitted PSR sponsorship of conferences[40]. Attending physicians and physician specialists had more PSR interactions and received higher numbers of medical samples and promotional material than residents[9,42]. Participants working in private practice alone or in both sectors were more likely to receive gifts than physicians working in the public sector [42,50]. Physicians in academic or hospital-based practice settings had less PSR interactions and significantly lower prescribing costs than physicians in nonacademic and nonhospital practices[38]. Most common gifts received were medical samples[9,21,22,31,36,37,42,63], promotional material[9,34,42] invitations for dinners[9], invitations for CMEs[22,34], scientific journals[34] and free lunches[21,37].

Perspectives of physicians towards PSR interactions

We found that physicians have a positive attitude towards PSRs[1, 13, 19, 20, 22, 31, 32, 40, 49, 58, 64] Physicians perceived PSRs as important sources of education and funding[10, 22, 32, 43, 45, 46]; while some studies reporting skeptical attitudes about the contribution of PSRs towards teaching and education[21, 36, 39, 40, 49]. Conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models, and free drug samples were

considered as appropriate gifts[19, 39, 51, 58]. Most of the physicians considered pharmaceutical information provided by PSRs, industry sponsored conferences and CME events as important instruments for enhancing their scientific knowledge[22, 32, 45, 46]. Compared to senior residents, significantly more junior residents felt that pharmaceutical representatives have a valuable teaching role [10].

Most of the physicians considered themselves immune to the influence of gifts[1, 10, 32, 33, 35, 37, 43, 59]. We found that better scores on knowledge and attitudes were significantly associated with lesser number of interactions with representatives and their gifts[19]. Most studies found that physicians do not believe that PSR interactions impact their prescribing behavoir,[1, 9-13, 65, 66], while other studies found that there was some extent of influence[21, 22, 34, 36, 37, 39, 43]. In addition, physicians considered their colleagues more susceptible than themselves to PSR marketing strategies[1, 20, 21, 37, 43]. There was a strong correlation between the amount of gifts and the belief that PSR interactions did not influence their prescribing behavior [10].

Gifts

Most common gifts received were medical samples[9, 21, 22, 31, 36, 37, 42-44, 47], promotional material[9, 34, 42, 67] invitations for dinners[9] and scientific journals[34].

Drug samples

Most of the physicians who accepted drug samples had a positive attitude towards the pharmaceutical representatives[9, 21, 22, 31, 36, 37, 42, 43]. Accepting samples lead to higher branded drug prescription rather than generic prescribing [22,47].

Pharmaceutical representative speakers

Sponsored lectures/symposia of pharmaceutical companies influenced behavior of the attendees leading to the attendees prescribing more drugs from the sponsoring companies without sufficient evidence supporting superiority of those drugs[56,57]. The majority of attending physicians failed to identify inaccurate information about the company drug[18].

Honoraria and Research Funding

Physicians who received money to attend pharmaceutical symposia or to perform research requested formulary addition of the company's drug more often than other physicians, This association was independent of many confounding factors[61] (Table 2). Brief encounters with PSRs and receipt of honoraria or research support were predictors of faculty requested

change in hospital formulary[68].

Conference travel

Pharmaceutical company sponsored conference travels to touristic locations have quantifiable impact on the prescribing rational of attendees. A significant increase (three times) in the prescribing rate of two company drugs was observed after the physicians attended a company sponsored symposium with all their expenses covered. Despite this significant difference in the prescribing patterns, physicians insisted there was no impact on their prescribing behaviour.[57]

Industry paid lunches

Most physicians received invitations for dinners[9] and free lunches[10, 21, 35, 43] . Clerks, interns and junior residents attended more company sponsored lunches than senior residents [10]. Pharmaceutical companies also sponsored departmental lunches during journal clubs[39]. There was no significant association between attending industry paid lunches[37] and dinners[9] and formulary request for that company's drug (Table 2).

#	Attitudes	Prescribing behavior	Knowledge	Formulary requests	Quality of Evidence (GRADE)
Gifts	Receiving higher number of gifts associated with belief that PRs 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 with PRS	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, 69].

CME sponsorship

Physicians who attended company sponsored CME events had more positive attitudes towards and inclination to prescribe the branded drugs[28, 34, 43, 67, 70-72]. We found that physicians who refused CME sponsorship were seen to prescribe higher proportion of generics and lower expenditure medicines when compared to physicians who attended CMEs[22].

Discussion

We report that there is widespread interaction between the pharmaceutical industry and physicians[9-11, 13, 42, 50]. Interactions are in the form of personal communications, free gifts such as drug samples, sponsored meals, sponsored conference travel, funding for research and CMEs and honoraria[9, 21, 22, 31, 36, 42]. The frequency of these interactions is comparable

between residents and physicians[10, 21, 22, 36, 42]. However, the amount and type of gifts vary with the position of the physician in medical hierarchy, specialization and location of practice[10, 13, 31, 38, 42, 43, 50, 58, 62]. In general, trainees (residents, interns) are treated with more drug samples, stationery items and free meals than senior physicians[10,13]. Senior physicians usually avail of sponsored conferences/ trips, research funding, honoraria and CME events. The extent of these interactions varies with academic versus non-academic institutions: non-academic hospitals record more interactions than others[31, 38, 42, 50, 55]. The majority of the physicians do not believe that they are affected by PSR interactions[1, 10, 32, 33, 35, 37, 43, 59] . However, a sizeable percentage in various surveys responded in the affirmative when asked whether they thought that their peers are vulnerable[1, 20, 21, 37, 43].

We observe that there is a positive correlation between acceptance of gifts and physicians' urge to reciprocate favorably towards the benefactor[12,22,47, 73, 74] Considering that physicians have a social contract with society at large to provide unbiased and altruistic service, this is an alarming observation. In 2005 a joint report by the WHO and Health Action International (HAI) reported on interventions to counter promotional activities.[75] The evidence presented in that report was not eligible for our systematic review, mostly because it related to interventions on students or residents. Nevertheless, the findings suggested that interventions such as industry self-regulation and guidelines for sales representatives are not effective, while education about drug promotion might influence physician attitudes[76-78].

Policies and educational intervention

The relationship of physicians with patients is of a fiduciary nature. Hence activities that might affect that relationship by altering physicians' clinical behavior are not acceptable. Physician-PSR interactions may put the trust of patients in physicians at risk. Interaction with PSRs begins early in the physicians' career. Trainees are exposed to PSR marketing and promotional techniques from the initial years of their medical education, which impact their prescribing behavior in future. Overall, trainees, i.e., residents and interns, are more vulnerable to PSR interactions than senior physicians[11, 41, 62] Physicians are susceptible to PSR interactions, which influences their clinical decision-making leading to greater prescriptions of branded drugs over low cost generic medicines and increasing healthcare cost[22, 47, 52, 53, 69] Therefore, there is need to institute and implement stringent policies curtailing physician-PSR relationships, as well as educational programs to increase awareness. Previous reports have indicated that implementing policies and conducting

educational programs are effective in increasing awareness of physician's attitudes towards PSR interactions[54, 59, 60, 76, 79-83]

Strengths and Limitations of the study

A major strength of this study is that is a large up-to-date systematic review of studies exploring the effects of physician and pharmaceutical industry representative interactions and residents in different settings (e.g. academic, primary care). Another strength of this study is the use of Cochrane and GRADE methodologies for conducting a review and assessing the quality of the studies. Moreover, we performed an extensive search in 3 databases and the grey literature. Some of the limitations of this review are related to the included studies, as some did not provide evidence for the significance of their findings or had varying study designs and outcomes, which made it impossible to conduct a meta-analysis. Also, the included studies were subject to risk of bias related to the lack of validity of outcome measurement, and inadequate handling of significant potential confounders.

Future implications

PSR interactions compromise the objectivity of the physicians. Educating physicians and increasing regulation of PSR interactions may lower the likelihood of prescribing new non-superior industry drugs and irrational prescription behavior. Further studies are required to evaluate the impact of PSR interactions on physicians over time and the benefits of various intervention based education programs on the clinical and ethical behavior of the physicians.

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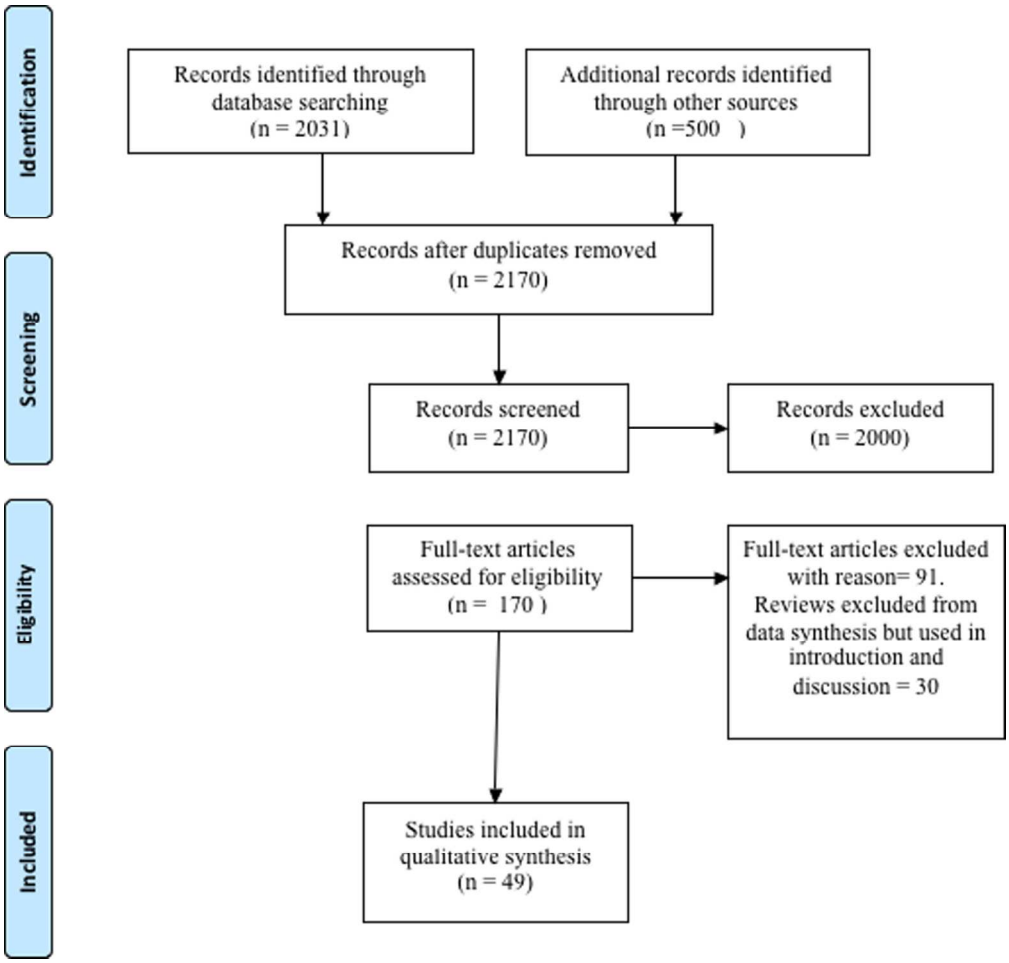
Legends

Figure 1: PRISMA flow diagram showing search strategy and included studies

Table 1: Characteristics of included studies

Table 2: Impact of physician-pharmaceutical industry interaction on physician



Flow diagram of study selection.

Search strategy for PubMed search engine of Medline

In an attempt to find all related literature on the topic, studies related to physician-pharmaceutical representative interactions that affect the prescribing behavior of the physicians were identified through computerized searches using, but not limited to, the following subject headings and text words in PubMed from 1992 to 2016.

1. Physician interactions with pharmaceutical industry
2. Physician attitude towards pharmaceutical representatives
3. Behavior of physicians towards pharmaceutical representatives
4. Gifts AND physician AND pharmaceutical representatives
5. Honoraria AND physician AND pharmaceutical representatives
6. Continuing medical education AND physician AND pharmaceutical representatives
7. Research funding AND physician AND pharmaceutical representatives
8. Conference travel AND physician AND pharmaceutical representatives
9. Industry sponsored meals AND physician behavior

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3/4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Association between pharmaceutical industry and its sales representatives' interactions on physicians' attitudes and prescribing habits: A systematic review

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Secondary Subject Heading:	Patient-centred medicine
Keywords:	Change management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Association between pharmaceutical industry and its sales representatives' interactions on physicians' attitudes and prescribing habits: A systematic review

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All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

Contributor Statement: All authors have contributed equally and have substantial contributions to the conception or design of the work; Author Freek Fickweiler for the acquisition, analysis, and interpretation of data for the work; Author Freek Fickweiler for drafting the work and Authors Ewout Urbach and Ward Fickweiler for revising it critically for important intellectual content; and all authors (Freek Fickweiler, Ward Fickweiler and Ewout Urbach) contributed to final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interest: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

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Data sharing statement: any data relevant to a published article will be made available alongside the article when published.

Abstract

Objectives

The objective of this review is to explore the frequency of physician and pharmaceutical industry and its sales representatives interactions and their impact on physicians' attitude, knowledge and behavior.

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, randomized 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, their prescribing behavior and increases 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 pharmaceutical sales representatives have been found to affect physicians' prescribing behavior 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 the 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 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

Keywords: pharmaceutical sales representative; physicians, drug industry; brand prescriptions; conflict of interest ;physicians-industry interactions; pharmaceutical industry; attitude of health personnel; gifts to physicians; medical education; irrational prescriptions

Introduction

The relationship between physicians and the pharmaceutical industry has evoked heated debate for many decades[1]. In 2012, the pharmaceutical industry spent $89.5 billion on physician-pharmaceutical sales representative (PSR) interactions which accounted for 60% of the global sales and marketing spending[2-8]. Previous reports have demonstrated that PSRs may influence prescribing behavior[9-16]. However, the evidence determining whether or not 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 on the other hand believe their colleagues are more susceptible to pharmaceutical industry marketing strategies than themselves [19-22]. The majority of the physicians do not believe that they are affected by pharmaceutical industry and PSR interactions. Most medical and governmental institutions have installed guidelines and self-regulatory and legislative checks to regulate the relationship between physicians and the pharmaceutical industry and its representatives t[5,15,16, 23-26]. However, while administrative proposals for deregulatory reforms that would remove some governmental authority over the industry are increasing, scientific evidence rigorously examining the extent of interactions between physicians and pharmaceutical industry and it PSRs is needed. This review evaluates e critically and systemically the evidence on the impact of pharmaceutical industry and PSR interactions on physicians.

Methodology

Protocol

We followed a detailed methodology that we described in our review protocol, which is available upon request to the corresponding author. Two independent reviewers assessed selected articles as per inclusion/exclusion criteria, shortlisted them for writing the review and cross-checked their decisions about inclusion/exclusion with each other. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1).

Eligibility criteria

The eligibility criteria were:

- Types of studies: cross sectional studies, cohort studies, randomized trials and survey designs comparing an intervention of interest on at least one facet of extent, impact on behavior and attitude.
- Types of participants: physicians, pharmaceutical representatives, physicians in training/residents. We did not consider medical students or other health professionals.
- Types of exposure: any type of interaction between physicians and the pharmaceutical industry where there is direct interaction with the physician, such as meeting with drug representatives, participating in pharmaceutical-sponsored CME event, receiving travel funding, free drug samples, industry-provided meals, gifts to the individual and active presentation of industry-related information to the physician
- Types of outcome: knowledge of physicians (e.g. accuracy of knowledge related to a specific medication), beliefs and/or attitudes of physicians regarding physician-industry interactions (e.g. perceived influence of information from the pharmaceutical company on their behavior), behavior of physicians (e.g. prescribing quantity/frequency)
- Type of control: no interaction.
- Exclusion criteria were: qualitative, ecological, econometric studies, editorials, letters to the editor, studies on medical students, small samples sizes, studies assessing non-targeted or indirect interactions (e.g. journal advertisement) and research funding.

We did not exclude studies based on risk of bias. We took risk of bias into account when grading the quality of evidence using GRADE approach.

Search strategy

The search strategy included Pubmed, Embase, Cochrane library and Google scholar electronic databases (January 1992 to August 2016). Databases were not searched before 1992, as these studies were already investigated in an earlier review[27]. The search combined terms for physicians and pharmaceutical, and included both free text words and medical subject heading relevant to the topic. We did not use a search filter. The supplementary information file provides the full details for one database. Additional search strategies included a search of the grey literature (theses and dissertations). Also, we reviewed the references lists of included and relevant papers.[27-29]

Assessment of risk of bias in included studies

Two reviewers assessed in duplicate and independently the riskof bias in each eligible study. Disagreements were resolved by discussion or adjudication by a third reviewer. We used the recommendations outlined in the Cochrane Handbook to assess the risk of bias in randomized studies. We graded each potential source of bias and rated the studies as high, low or unclear risk of bias.

Data analysis and synthesis

The information extracted from the selected studies included type of study, study design, type of pharmaceutical industry and PSR interaction and type of outcome. We did not conduct a meta-analysis due to the heterogeneity of study design, types of interventions, outcomes assessed, and outcome measures used. Instead, we summarized the data narratively. We assessed the quality of evidence by outcome using the GRADE methodology[30].

Results

We independently screened the titles and abstracts of the 2170 identified records for potential eligibility. Out of 2170, the full text of 49 eligible citations which matched the inclusion criteria were retrieved and used for qualitative assessment during the writing of the review (Figure 1, Table 1)

Study	Authors	Country	Timeframe	Participants, setting	Study design	Interaction	Outcomes
1	Steinman et al., 2001	USA	Spring 1999	Surveys about attitudes and behaviors toward industry gifts in 105 residents at a university-based internal medicine residency program	Cross-sectional	PSR interactions, gifts	Most participants (61%) hold positive attitudes toward gifts from industry and PSR interactions and believe they do not influence their own prescribing, but only 16% believed other physicians were

							similarly unaffected (P< .0001)
11	De Ferrari et al., 2014	Peru	March 2013	Questionnaire in 155 faculty and trainee physicians of five different clinical departments working in a public general hospital	Cross-sectional	PSR interactions, medical samples, promotional material, dinners	Positive attitude towards representatives (88.5% of participants). Faculty physicians received a larger amount of medical samples and promotional material and were more prone to believe that gifts and lunches do not influence their prescribing behavior (42.2% vs. 23.6%; p=0.036)
12	Thomson et al., 1994	New Zealand	1991	Questionnaire survey of 67 general practitioners	Cross-sectional	Interactions with PSR	Most general practitioners (67%) had a negative attitude toward PSR interaction
13	Kamal et al., 2015	Egypt	July and August 2013	Interviews with 18 physicians	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
14	Hodges, 1995	Canada	October 1993-February 1994	Survey in 105 residents of psychiatry	Cross-sectional	Interaction with PSR, drug samples, lunches	Positive attitude towards PSR interaction (56.5% of participants). The more money and

							promotional items a participant had received, the more likely he or she was to believe that discussions with representatives did not affect prescribing ($p < 0.05$)
15	Gibbons et al., 1998	USA	Not reported	Survey of 392 physicians in two tertiary-care medical centers	Cross-sectional	PSR interactions,gifts, samples, travel, lunches	Positive attitude towards PSR interactions, gifts, samples and lunches
16	Spingarn et al., 1996	USA	February 1990	75 internal medicine physicians in university medical center	Retrospective cohort	PSR interaction (teaching)	Attendees inappropriately prescribed PSR speakers drug compared to non-attendees ($p=0.029$)
17	Zaki, 2014	Saudi Arabia	September-November 2013	Survey of 250 physicians	Randomized, cross-sectional survey	Conferences, drug samples	Favorable towards promotion
18	Orlowski et al., 1994	USA	1987-1989	10 physicians that were invited for a symposium and tracking the pharmacy inventory usage reports for these drugs before and after the symposia	Cohort	Conference travel	Significant increase in the prescribing pattern of drugs occurred following the symposia ($p<0.001$)

19	Scheffer et al., 2014	Brazil	2007-2009	Survey of 300 physicians prescribing antiretroviral drugs	Cross-sectional	Interaction with representative, drug samples, journals	Frequency of interaction; the majority of (64%) of the physicians had multiple forms of interactions with PSR
20	Brett et al., 2003	USA	Not reported	Questionnaire of 93 physicians in a medical school	Cross-sectional	Interaction with PSR	Impact on attitudes; most physicians believed that most of PSR activities do not pose major ethical problems
21	Gupta et al., 2016	India	June-September 2014	Survey of 81 physicians in single hospital	Cross-sectional	Interaction with representative, drug samples, journals	Impact on prescribing; 61.7% of participants think that PSR has an impact on their prescribing (P = 0.0001)
22	Morgan et al., 2006	USA	March 2003	Survey of 397 obstetrician-gynaecologists	Cross-sectional	Drug samples, promotional material, lunch	Impact on prescribing, positive attitudes; most respondents thought it's proper to accept drug samples (92%), lunch (77%), an anatomical model (75%) or a well-paid consultantship (53%) from PSR
23	Alosaimi	Saudi	2012	Survey of	Cross-	Interaction	Positive

	et al., 2014	Arabia		659 physicians	sectional	with PSR	attitude towards PSR interaction
24	Chren et al., 1994	USA	1989-1990	40 case physicians and 80 control physicians	Case control	PSR interactions, honoraria, research	Increased prescription of company's drug after PSR interaction, honoraria and research ($p<0.001$, all)
25	Randall et al., 2005	USA	October 2001	Intervention group of physicians (n=18) that received education about PSR interaction and control group (n=14)	Controlled trial	Interaction with PSR	The majority of residents found the interactions and gifts useful. Compared to the comparison group, the intervention group significantly decreased the reported number of office supplies and noneducational gifts ($p<0.05$)
26	Caudil et al., 1996	USA	Not reported	Survey of 446 primary care physicians	Cross-sectional	Interaction with PSR	Significant positive correlation between physician cost of prescribing and perceived credibility, availability, applicability, and use of information provided by PSR ($p < 0.01$)

27	Andaleeb et al., 1995	USA	Not reported	223 physicians in northwestern Pennsylvania	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
28	Reeder et al., 1993	USA	1991-1992	87 residents of emergency medicine	Cross-sectional	Interaction with PSR, gifts	Most participants believed that PSR interaction had no impact on their prescribing
29	Lichstein et al., 1992	USA	January-March 1990	272 directors of internal medicine residency programs	Cross-sectional	Interaction with PSR	Most participants had a positive attitude towards PSR interactions
30	Brotzman et al., 1992	USA	Not reported	Directors of 386 family practice residency programs	Cross-sectional	Interaction with PSR	Majority of programs do not have guidelines for interaction with PSR
31	Alssageer et al., 2012	Libya	August-October 2010	Survey of 608 physicians in public and private practice settings	Cross-sectional	Interaction with PSR, drug samples, printed materials	Positive attitude towards PSR interactions
32	Lieb & Brandtonies, 2010	Germany	2007	Survey of 208 physicians (neurology, cardiology and general medicine)	Cross-sectional	Interaction with PSR, drug samples, printed materials, lunches	Frequency and impact on attitudes
33	Lieb & Scheurich, 2014	Germany	2010-2011	Survey of 160 physicians in private and public practices	Cross-sectional	Interaction with representative, drug samples, printed materials, CME	High expenditure prescribing; avoidance of industry-sponsored CME is associated with more

							rational prescribing habits
34	Lieb & Koch, 2013	Germany	May-July 2012	Survey of 1038 medical students at 8 universities	Cross-sectional	Interaction with representative, drug samples, printed materials, lunches	Most participants have contact with the pharmaceutical company; 24.6% of the participants thought gifts would influence their future prescribing behavior, while 45.1% thought gifts would influence their classmates' future prescribing behavior ($p<0.001$)
35	Brown et al., 2015	USA	2008 and 2013	251 directors of family medicine residency programs	Cross-sectional	Interaction with PSR, gifts, lunches	Negative attitude towards PSR interactions
37	Rahmana et al., 2015	Bangladesh	December 2008-January 2009	Survey of 83 village physicians	Cross-sectional	Interaction with PSR	Impact on their prescribing
38	Lee & Begley, 2016	USA	2008	Nationally representative survey of 4720 physicians	Cross-sectional	Gifts	Gifts were associated with lower perceived quality of patient care; an inverse relationship between the frequency of received gifts and the perceived quality of care was

							observed
39	Montastruc et al., 2014	France	August-October 2011	Survey among 631 medical residents	Cross-sectional	Interaction with representative	Most participants believed that PSR interaction had no impact on their prescribing; participants who had a more positive opinion were more frequently exposed to PSR ($p<0.001$)
40	Ketis & Kersnik, 2013	Slovenia	October 2011	895 family physicians at the primary level of care	Cross-sectional	Interaction with PSR	Positive effect on knowledge; Participants value PSRs' selling and communication skills and trustworthiness highly
41	Hurley et al., 2014	USA	2010	3500 dermatologists	Cross-sectional	Free drug samples	Impact on their prescribing; the provision of samples with a prescription by dermatologists has been increasing over time, and this increase is correlated ($r = 0.92$) with the use of the branded generic drugs promoted by

							these sample
42	Makowska, 2014	Poland	November-December 2008	Survey of 382 physicians	Cross-sectional	Gifts	Positive attitude towards PSR interactions
43	Siddiqui et al., 2014	Pakistan	Not reported	Questionnaires of 352 medical students	Cross-sectional	Interaction with representative	Positive attitude towards PSR interaction
55	Workneh BD et al., 2016	Ethiopia	February-March 2015	Survey of 90 physicians from public and private health facilities	Cross-sectional	Interaction with representative, gifts	Positive attitude towards industry, impact on prescribing behavior; Nearly half of the physicians reported that their prescribing decisions were influenced by PSR
57	Khan N et al., 2016	Pakistan	Not reported	Questionnaires in 472 physicians	Cross-sectional	Interaction with representative, gifts	Positive attitude towards PSR interaction
58	Saito S et al. 2010	Japan	January-March 2008	1417 physicians working in internal medicine, general surgery, orthopedic surgery, pediatrics, obstetrics-gynecology, psychiatry, and ophthalmology	National Survey	Interaction with industry, receipt of gifts, funds, CME, samples	Positive attitude towards PSR and gifts, value information from PSR, interactions higher with physicians who prefer to prescribe brand names
59	Ziegler MG et al. 1995	USA	1993	27 physicians working in public and	Survey	Accuracy of information provided by PSRs about	Incorrect information often provided by

				private hospitals		drugs	speakers goes unnoticed by physicians
60	Lurie N et al., 1990	USA	Not reported	240 internal medicine faculty physicians in academic medical centers	Survey	Effect of interaction with PSR, free meals, honoraria and research support	Impact on prescribing behavior and formulary change requests
62	DeJong C et al., 2016	USA	August-September 2013	279.669 physicians who wrote Medicare prescriptions in any of 4 drug classes: statins, cardioselective β-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ACE inhibitors and ARBs), and selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs) Physicians	Cross-sectional	Industry sponsored meals	Receipt of industry-sponsored meals was associated with an increased rate of brand name prescription.
63	Yeh JS et al., 2016	USA	2011	All licensed Massachusetts physicians who wrote prescriptions for statins paid for	Cross-sectional	Effect of industry payment on prescription of branded drugs for cholesterol control	Payment for meals and educational programs increased prescription of brand name

				under the Medicare drug benefit in 2011 (n=2444)			statins.
65	Bowman MA et al., 1988	USA	Not reported	121 physician attendees	Self report survey	Effect of CME on prescribing behavior	Sponsoring company's drugs were favored during prescription
66	Fischer MA et al., 2009	USA	November 2006-March 2007	Multi-disciplinary focus groups with 61 physicians	Survey	Effect of industry marketing strategies on prescription and cognitive dissonance of physicians	Most participants reported no PSR impact on their prescribing, value to have ability to evaluate information of PSRs
67	Chimonas S et al., 2007	USA	June 2004	Six focus groups in 32 academic and community physicians	Survey	PSR interactions	Positive attitude towards PSR interaction
72	Yeh JS et al., 2014	USA	Not reported	1610 US medical students	Cross-sectional	Interaction with representative, gifts, lunches	Policies separating students from representatives reduced number of interactions
73	Larkin I et al., 2014	USA	January 2006-June 2009	Pediatricians, child & adolescent psychiatrists in five medical centers	Survey	Interaction with PSR	Anti detailing policies reduced the prescription of off-label antidepressants and anti psychotics for children
74	Esmaily HM et al., 2010	Iran	Not reported	112 general physicians were randomized in two groups: 1) outcome-	Randomized trial	Effect of outcome and retinal prescribing	Rational prescribing improved in some of the important outcome-based

				based educational intervention for rational prescribing and 2) concurrent CME program in the field of rational prescribing			indicators. No difference between two arms of the study
76	Parikh K et al., 2016	USA	2014	descriptive, cross-sectional analysis of Open Payments data and 9 638 825 payments to physicians and pediatricians from January 1 to December 31, 2014	Cross-sectional	Comparison of PSR interactions between pediatricians and other specialists; among subspecialities of pediatrics.	Pediatricians get fewer gifts from PSR than internists. There is variation among sub specialities for extent of interaction.
78	Chressanthis GA et al. 2012	USA	Not reported	Clinical decisions of 72,114 physicians were statistically analyzed using prescription data	Survey	Effect of restricting PSRs on clinical practice and knowledge	Restricting PSRs affected information flow about drugs, both negative and positive.

We excluded 2000 records as they were not relevant (n = 1641), not original research (n=269), about medical students (n=4) and non-medical (e.g. ecological, econometric; n=86).

Characteristics of included studies

The identified studies were published between 1992 and August 2016. Most of the studies included were cross-sectional studies[1,9-13,19,21,22,31-55]. Only two studies were cohort studies[56, 57], three were randomized trials[58-60] and one study was a case-control study[61].

Extent of interactions between physicians and the pharmaceutical industry

We found that PSR interactions are a regular feature in the daily lives of physicians across the world [9-11,13,42,50]. Most of the attending physicians and residents have at least one interaction

with industry representatives per month [10,21,22,36,42]. The frequency of interactions or gifts offered and accepted varies with private versus public hospital setting and the position of the physicians in the medical hierarchy [10,13,31,38,42,43,50,58,62]. Junior residents received twice as much free drug samples from PSR interactions than senior residents [10]. PSR interactions were significantly higher at the beginning of residency[13]. The majority of program directors of internal medicine residencies in the USA allowed PSRs to meet with residents during working hours and permitted PSR sponsorship of conferences[40]. Attending physicians and physician specialists had more PSR interactions and received higher numbers of medical samples and promotional material than residents[9,42]. Participants working in private practice alone or in both sectors were more likely to receive gifts than physicians working in the public sector [38,42,50].. Most common gifts received were medical samples[9,21,22,31,36,37,42,63], promotional material[9,34,42] invitations for dinners[9], invitations for CMEs[22,34], scientific journals[34] and free lunches[21,37].

Perspectives of physicians towards PSR interactions

We found that physicians have a positive attitude towards PSRs[1, 13, 19, 20, 22, 31, 32, 40, 49, 58, 64] Physicians perceived PSRs as important sources of education and funding[10, 22, 32, 43, 45, 46]; while some studies reporting skeptical attitudes about the contribution of PSRs towards teaching and education[21, 36, 39, 40, 49]. Conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models, and free drug samples were considered as appropriate gifts[19, 39, 51, 58]. Most of the physicians considered pharmaceutical information provided by PSRs, industry sponsored conferences and CME events as important instruments for enhancing their scientific knowledge[22, 32, 45, 46]. Compared to senior residents, significantly more junior residents felt that pharmaceutical representatives have a valuable teaching role [10].

Most of the physicians considered themselves immune to the influence of gifts[1, 10, 32, 33, 35, 37, 43, 59]. Most studies found that physicians do not believe that PSR interactions impact their prescribing behavoir,[1, 9-13, 65, 66], while other studies found that there was some extent of influence[21, 22, 34, 36, 37, 39, 43]. In addition, physicians considered their colleagues more susceptible than themselves to PSR marketing strategies[1, 20, 21, 37, 43]. There was a strong correlation between the amount of gifts and the belief that PSR interactions did not influence their prescribing behavior [10].

Gifts

We found that better scores on knowledge and attitudes were significantly associated with fewer interactions with representatives and their gifts[19]. Most common gifts received were medical samples[9, 21, 22, 31, 36, 37, 42-44, 47], promotional material[9, 34, 42, 67] invitations for dinners[9] and scientific journals[34]

Drug samples

Most of the physicians who accepted drug samples had a positive attitude towards the pharmaceutical representatives[9, 21, 22, 31, 36, 37, 42, 43]. Accepting samples lead to higher branded drug prescription rather than generic prescribing [22,47].

Pharmaceutical representative speakers

Sponsored lectures/symposia of pharmaceutical companies influenced behavior of the attendees leading to the attendees prescribing more drugs from the sponsoring companies without sufficient evidence supporting superiority of those drugs[56,57]. The majority of attending physicians failed to identify inaccurate information about the company drug[18].

Honoraria and Research Funding

Physicians who received money to attend pharmaceutical symposia or to perform research requested formulary addition of the company's drug more often than other physicians, This association was independent of many confounding factors[61] (Table 2). Brief encounters with PSRs and receipt of honoraria or research support were predictors of faculty requested change in hospital formulary[68].

Conference travel

Pharmaceutical company sponsored conference travels to touristic locations have quantifiable impact on the prescribing rational of attendees. A significant increase (three times) in the prescribing rate of two company drugs was observed after the physicians attended a company sponsored symposium with all their expenses covered. Despite this significant difference in the prescribing patterns, physicians insisted there was no impact on their prescribing behaviour.[57]

Industry paid lunches

Most physicians received invitations for dinners[9] and free lunches[10, 21, 35, 43] . Clerks, interns and junior residents attended more company sponsored lunches than senior residents [10]. Pharmaceutical companies also sponsored departmental lunches during journal clubs[39]. There was no significant association between attending industry paid lunches[37] and dinners[9] and formulary request for that company's drug (Table 2).

#	Attitudes	Prescribing behavior	Knowledge	Formulary requests	Quality of Evidence (GRADE)
Gifts	Receiving higher number of gifts associated with belief that PRs 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 with PRS	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, 69].

CME sponsorship

Physicians who attended company sponsored CME events had more positive attitudes towards and inclination to prescribe the branded drugs[28, 34, 43, 67, 70-72]. We found that physicians who refused CME sponsorship were seen to prescribe higher proportion of generics and lower expenditure medicines when compared to physicians who attended CMEs[22].

Discussion

We report that there is widespread interaction between the pharmaceutical industry and physicians[9-11, 13, 42, 50]. Interactions are in the form of personal communications, free gifts such as drug samples, sponsored meals, sponsored conference travel, funding for research and CMEs and honoraria[9, 21, 22, 31, 36, 42]. The frequency of these interactions is comparable between residents and physicians[10, 21, 22, 36, 42]. However, the amount and type of gifts vary with the position of the physician in medical hierarchy, specialization and location of practice[10, 13, 31, 38, 42, 43, 50, 58, 62]. In general, trainees (residents, interns) are treated with more drug samples, stationery items and free meals than senior physicians[10,13]. Senior physicians usually avail of sponsored conferences/ trips, research funding, honoraria and CME events. The extent of these interactions varies with academic versus non-academic institutions: non-academic hospitals record more interactions than others[31, 38, 42, 50, 55]. The majority of the physicians do not believe that they are affected by PSR interactions[1, 10, 32, 33, 35, 37, 43, 59] . However, a sizeable percentage in various surveys responded in the affirmative when asked whether they thought that their peers are vulnerable[1, 20, 21, 37, 43].

We observe that there is a positive correlation between acceptance of gifts and physicians' urge to reciprocate favorably towards the benefactor[12,22,47, 73, 74] Considering that physicians have a social contract with society at large to provide unbiased and altruistic service, this is an alarming observation. In 2005 a joint report by the WHO and Health Action International (HAI) reported on interventions to counter promotional activities.[75] The evidence presented in that report was not eligible for our systematic review, mostly because it related to interventions on students or residents. Nevertheless, the findings suggested that interventions such as industry self-regulation and guidelines for sales representatives are not effective, while education about drug promotion might influence physician attitudes[76-78].

Policies and educational intervention

The relationship of physicians with patients is of a fiduciary nature. Hence activities that might affect that relationship by altering physicians' clinical behavior are not acceptable. Physician-pharmaceutical industry and PSR interactions may put the trust of patients in physicians at risk. Interaction with pharmaceutical industry and PSRs begins early in the physicians' career. Trainees are exposed to pharmaceutical industry marketing and promotional techniques from the initial years of their medical education, which impact their prescribing behavior in future. Overall, trainees, i.e., residents and interns, are more vulnerable to pharmaceutical industry and PSR interactions than senior physicians[11, 41, 62] Physicians are susceptible to pharmaceutical industry and PSR interactions, which influences their clinical decision-making leading to greater prescriptions of branded drugs over low cost generic medicines and increasing healthcare cost[22, 47, 52, 53, 69] Therefore, there is need to institute and implement stringent policies curtailing physician-pharmaceutical industry and PSR relationships, as well as educational programs to increase awareness. Previous reports have indicated that implementing policies and conducting educational programs are effective in increasing awareness of physician's attitudes towards pharmaceutical industry and PSR interactions[54, 59, 60, 76, 79-83]

Strengths and Limitations of the study

A major strength of this study is that is a large up-to-date systematic review of studies exploring the effects of physician and pharmaceutical industry representative interactions and residents in different settings (e.g. academic, primary care). Another strength of this study is the use of Cochrane and GRADE methodologies for conducting a review and assessing the quality of the studies. Moreover, we performed an extensive search in 3 databases and the

grey literature. Some of the limitations of this review are related to the included studies, as some did not provide evidence for the significance of their findings or had varying study designs and outcomes, which made it impossible to conduct a meta-analysis. Also, the included studies were subject to risk of bias related to the lack of validity of outcome measurement, and inadequate handling of significant potential confounders.

Future implications

Pharmaceutical industry and PSR interactions compromise the objectivity of the physicians. Educating physicians and increasing regulation of pharmaceutical industry and PSR interactions may lower the likelihood of prescribing new non-superior industry drugs and irrational prescription behavior. Further studies are required to evaluate the impact of pharmaceutical industry and PSR interactions on physicians over time and the benefits of various intervention based education programs on the clinical and ethical behavior of the physicians.

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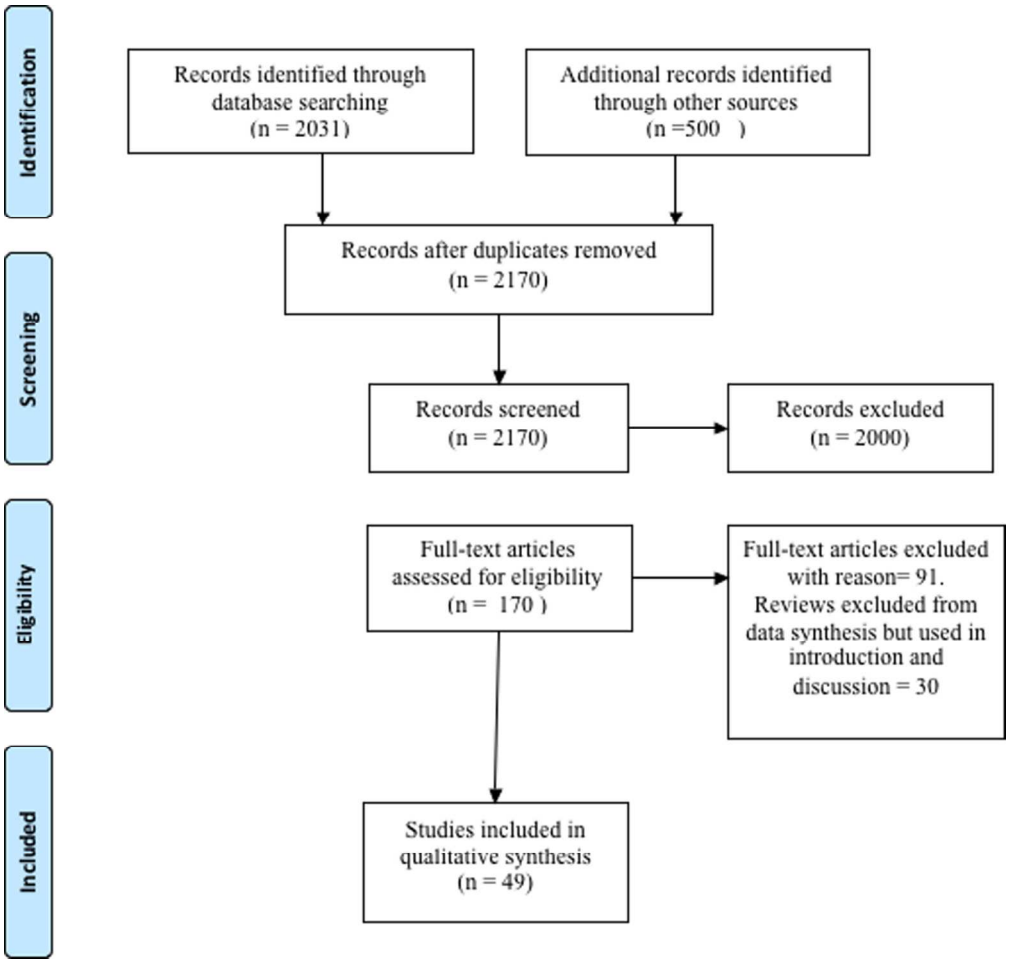
Legends

Figure 1: PRISMA flow diagram showing search strategy and included studies

Table 1: Characteristics of included studies

Table 2: Impact of physician-pharmaceutical industry interaction on physician



Flow diagram of study selection.

Search strategy for PubMed search engine of Medline

In an attempt to find all related literature on the topic, studies related to physician-pharmaceutical representative interactions that affect the prescribing behavior of the physicians were identified through computerized searches using, but not limited to, the following subject headings and text words in PubMed from 1992 to 2016.

1. Physician interactions with pharmaceutical industry
2. Physician attitude towards pharmaceutical representatives
3. Behavior of physicians towards pharmaceutical representatives
4. Gifts AND physician AND pharmaceutical representatives
5. Honoraria AND physician AND pharmaceutical representatives
6. Continuing medical education AND physician AND pharmaceutical representatives
7. Research funding AND physician AND pharmaceutical representatives
8. Conference travel AND physician AND pharmaceutical representatives
9. Industry sponsored meals AND physician behavior

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3/4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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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

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

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All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted workContributor Statement: All authors have contributed equally and have substantial contributions to the conception or design of the work; Author Freek Fickweiler for the acquisition, analysis, and interpretation of data for the work; Author Freek Fickweiler for drafting the work and Authors Ewout Urbach and Ward Fickweiler for revising it critically for important intellectual content; and all authors (Freek Fickweiler, Ward Fickweiler and Ewout Urbach) contributed to final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interest: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

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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, randomized 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, their prescribing behavior and increases 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 pharmaceutical sales representatives have been found to affect physicians' prescribing behavior 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 the 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 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

Keywords: pharmaceutical sales representative; physicians, drug industry; brand prescriptions; conflict of interest ;physicians-industry interactions; pharmaceutical industry; attitude of health personnel; gifts to physicians; medical education; irrational prescriptions

Introduction

The relationship between physicians and the pharmaceutical industry has evoked heated debate for many decades[1]. In 2012, the pharmaceutical industry spent $89.5 billion on physician-pharmaceutical sales representative (PSR) interactions which accounted for 60% of the global sales and marketing spending[2-8]. Previous reports have demonstrated that PSRs may influence prescribing behavior[9-16]. However, the evidence determining whether or not 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 on the other hand believe their colleagues are more susceptible to pharmaceutical industry marketing strategies than themselves [19-22]. The majority of the physicians do not believe that they are affected by pharmaceutical industry and PSR interactions. Most medical and governmental institutions have installed guidelines and self-regulatory and legislative checks to regulate the relationship between physicians and the pharmaceutical industry and its representatives t[5,15,16, 23-26]. However, while administrative proposals for deregulatory reforms that would remove some governmental authority over the industry are increasing, scientific evidence rigorously examining the extent of interactions between physicians and pharmaceutical industry and it PSRs is needed. This review evaluates e critically and systemically the evidence on the impact of pharmaceutical industry and PSR interactions on physicians.

Methodology

Protocol

We followed a detailed methodology that we described in our review protocol, which is available upon request to the corresponding author. Two independent reviewers assessed selected articles as per inclusion/exclusion criteria, shortlisted them for writing the review and cross-checked their decisions about inclusion/exclusion with each other. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1).

Eligibility criteria

The eligibility criteria were:

- Types of studies: cross sectional studies, cohort studies, randomized trials and survey designs comparing an intervention of interest on at least one facet of extent, impact on behavior and attitude.
- Types of participants: physicians, pharmaceutical representatives, physicians in training/residents. We did not consider medical students or other health professionals.
- Types of exposure: any type of interaction between physicians and the pharmaceutical industry where there is direct interaction with the physician, such as meeting with drug representatives, participating in pharmaceutical-sponsored CME event, receiving travel funding, free drug samples, industry-provided meals, gifts to the individual and active presentation of industry-related information to the physician
- Types of outcome: knowledge of physicians (e.g. accuracy of knowledge related to a specific medication), beliefs and/or attitudes of physicians regarding physician-industry interactions (e.g. perceived influence of information from the pharmaceutical company on their behavior), behavior of physicians (e.g. prescribing quantity/frequency)
- Type of control: no interaction.
- Exclusion criteria were: qualitative, ecological, econometric studies, editorials, letters to the editor, studies on medical students, small samples sizes, studies assessing non-targeted or indirect interactions (e.g. journal advertisement) and research funding.

We did not exclude studies based on risk of bias. We took risk of bias into account when grading the quality of evidence using GRADE approach.

Search strategy

The search strategy included Pubmed, Embase, Cochrane library and Google scholar electronic databases (January 1992 to August 2016). Databases were not searched before 1992, as these studies were already investigated in an earlier review[27]. The search combined terms for physicians and pharmaceutical, and included both free text words and medical subject heading relevant to the topic. We did not use a search filter. The supplementary information file provides the full details for one database. Additional search strategies included a search of the grey literature (theses and dissertations). Also, we reviewed the references lists of included and relevant papers.[27-29]

Assessment of risk of bias in included studies

Two reviewers assessed in duplicate and independently the riskof bias in each eligible study. Disagreements were resolved by discussion or adjudication by a third reviewer. We used the recommendations outlined in the Cochrane Handbook to assess the risk of bias in randomized studies. We graded each potential source of bias and rated the studies as high, low or unclear risk of bias.

Data analysis and synthesis

The information extracted from the selected studies included type of study, study design, type of pharmaceutical industry and PSR interaction and type of outcome. We did not conduct a meta-analysis due to the heterogeneity of study design, types of interventions, outcomes assessed, and outcome measures used. Instead, we summarized the data narratively. We assessed the quality of evidence by outcome using the GRADE methodology[30].

Results

We independently screened the titles and abstracts of the 2170 identified records for potential eligibility. Out of 2170, the full text of 49 eligible citations which matched the inclusion criteria were retrieved and used for qualitative assessment during the writing of the review (Figure 1, Table 1)

Study	Authors	Country	Timeframe	Participants, setting	Study design	Interaction	Outcomes
1	Steinman et al., 2001	USA	Spring 1999	Surveys about attitudes and behaviors toward industry gifts in 105 residents at a university-based internal medicine residency program	Cross-sectional	PSR interactions, gifts	Most participants (61%) hold positive attitudes toward gifts from industry and PSR interactions and believe they do not influence their own prescribing, but only 16% believed other physicians were

							similarly unaffected (P< .0001)
11	De Ferrari et al., 2014	Peru	March 2013	Questionnaire in 155 faculty and trainee physicians of five different clinical departments working in a public general hospital	Cross-sectional	PSR interactions, medical samples, promotional material, dinners	Positive attitude towards representatives (88.5% of participants). Faculty physicians received a larger amount of medical samples and promotional material and were more prone to believe that gifts and lunches do not influence their prescribing behavior (42.2% vs. 23.6%; p=0.036)
12	Thomson et al., 1994	New Zealand	1991	Questionnaire survey of 67 general practitioners	Cross-sectional	Interactions with PSR	Most general practitioners (67%) had a negative attitude toward PSR interaction
13	Kamal et al., 2015	Egypt	July and August 2013	Interviews with 18 physicians	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
14	Hodges, 1995	Canada	October 1993-February 1994	Survey in 105 residents of psychiatry	Cross-sectional	Interaction with PSR, drug samples, lunches	Positive attitude towards PSR interaction (56.5% of participants). The more money and

							promotional items a participant had received, the more likely he or she was to believe that discussions with representatives did not affect prescribing ($p < 0.05$)
15	Gibbons et al., 1998	USA	Not reported	Survey of 392 physicians in two tertiary-care medical centers	Cross-sectional	PSR interactions,gifts, samples, travel, lunches	Positive attitude towards PSR interactions, gifts, samples and lunches
16	Spingarn et al., 1996	USA	February 1990	75 internal medicine physicians in university medical center	Retrospective cohort	PSR interaction (teaching)	Attendees inappropriately prescribed PSR speakers drug compared to non-attendees ($p=0.029$)
17	Zaki, 2014	Saudi Arabia	September-November 2013	Survey of 250 physicians	Randomized, cross-sectional survey	Conferences, drug samples	Favorable towards promotion
18	Orlowski et al., 1994	USA	1987-1989	10 physicians that were invited for a symposium and tracking the pharmacy inventory usage reports for these drugs before and after the symposia	Cohort	Conference travel	Significant increase in the prescribing pattern of drugs occurred following the symposia ($p<0.001$)

19	Scheffer et al., 2014	Brazil	2007-2009	Survey of 300 physicians prescribing antiretroviral drugs	Cross-sectional	Interaction with representative, drug samples, journals	Frequency of interaction; the majority of (64%) of the physicians had multiple forms of interactions with PSR
20	Brett et al., 2003	USA	Not reported	Questionnaire of 93 physicians in a medical school	Cross-sectional	Interaction with PSR	Impact on attitudes; most physicians believed that most of PSR activities do not pose major ethical problems
21	Gupta et al., 2016	India	June-September 2014	Survey of 81 physicians in single hospital	Cross-sectional	Interaction with representative, drug samples, journals	Impact on prescribing; 61.7% of participants think that PSR has an impact on their prescribing (P = 0.0001)
22	Morgan et al., 2006	USA	March 2003	Survey of 397 obstetrician-gynaecologists	Cross-sectional	Drug samples, promotional material, lunch	Impact on prescribing, positive attitudes; most respondents thought it's proper to accept drug samples (92%), lunch (77%), an anatomical model (75%) or a well-paid consultantship (53%) from PSR
23	Alosaimi	Saudi	2012	Survey of	Cross-	Interaction	Positive

	et al., 2014	Arabia		659 physicians	sectional	with PSR	attitude towards PSR interaction
24	Chren et al., 1994	USA	1989-1990	40 case physicians and 80 control physicians	Case control	PSR interactions, honoraria, research	Increased prescription of company's drug after PSR interaction, honoraria and research ($p<0.001$, all)
25	Randall et al., 2005	USA	October 2001	Intervention group of physicians (n=18) that received education about PSR interaction and control group (n=14)	Controlled trial	Interaction with PSR	The majority of residents found the interactions and gifts useful. Compared to the comparison group, the intervention group significantly decreased the reported number of office supplies and noneducational gifts ($p<0.05$)
26	Caudil et al., 1996	USA	Not reported	Survey of 446 primary care physicians	Cross-sectional	Interaction with PSR	Significant positive correlation between physician cost of prescribing and perceived credibility, availability, applicability, and use of information provided by PSR ($p < 0.01$)

27	Andaleeb et al., 1995	USA	Not reported	223 physicians in northwestern Pennsylvania	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
28	Reeder et al., 1993	USA	1991-1992	87 residents of emergency medicine	Cross-sectional	Interaction with PSR, gifts	Most participants believed that PSR interaction had no impact on their prescribing
29	Lichstein et al., 1992	USA	January-March 1990	272 directors of internal medicine residency programs	Cross-sectional	Interaction with PSR	Most participants had a positive attitude towards PSR interactions
30	Brotzman et al., 1992	USA	Not reported	Directors of 386 family practice residency programs	Cross-sectional	Interaction with PSR	Majority of programs do not have guidelines for interaction with PSR
31	Alssageer et al., 2012	Libya	August-October 2010	Survey of 608 physicians in public and private practice settings	Cross-sectional	Interaction with PSR, drug samples, printed materials	Positive attitude towards PSR interactions
32	Lieb & Brandtonies, 2010	Germany	2007	Survey of 208 physicians (neurology, cardiology and general medicine)	Cross-sectional	Interaction with PSR, drug samples, printed materials, lunches	Frequency and impact on attitudes
33	Lieb & Scheurich, 2014	Germany	2010-2011	Survey of 160 physicians in private and public practices	Cross-sectional	Interaction with representative, drug samples, printed materials, CME	High expenditure prescribing; avoidance of industry-sponsored CME is associated with more

							rational prescribing habits
34	Lieb & Koch, 2013	Germany	May-July 2012	Survey of 1038 medical students at 8 universities	Cross-sectional	Interaction with representative, drug samples, printed materials, lunches	Most participants have contact with the pharmaceutical company; 24.6% of the participants thought gifts would influence their future prescribing behavior, while 45.1% thought gifts would influence their classmates' future prescribing behavior ($p<0.001$)
35	Brown et al., 2015	USA	2008 and 2013	251 directors of family medicine residency programs	Cross-sectional	Interaction with PSR, gifts, lunches	Negative attitude towards PSR interactions
37	Rahmana et al., 2015	Bangladesh	December 2008-January 2009	Survey of 83 village physicians	Cross-sectional	Interaction with PSR	Impact on their prescribing
38	Lee & Begley, 2016	USA	2008	Nationally representative survey of 4720 physicians	Cross-sectional	Gifts	Gifts were associated with lower perceived quality of patient care; an inverse relationship between the frequency of received gifts and the perceived quality of care was

							observed
39	Montastruc et al., 2014	France	August-October 2011	Survey among 631 medical residents	Cross-sectional	Interaction with representative	Most participants believed that PSR interaction had no impact on their prescribing; participants who had a more positive opinion were more frequently exposed to PSR ($p<0.001$)
40	Ketis & Kersnik, 2013	Slovenia	October 2011	895 family physicians at the primary level of care	Cross-sectional	Interaction with PSR	Positive effect on knowledge; Participants value PSRs' selling and communication skills and trustworthiness highly
41	Hurley et al., 2014	USA	2010	3500 dermatologists	Cross-sectional	Free drug samples	Impact on their prescribing; the provision of samples with a prescription by dermatologists has been increasing over time, and this increase is correlated ($r = 0.92$) with the use of the branded generic drugs promoted by

							these sample
42	Makowska, 2014	Poland	November-December 2008	Survey of 382 physicians	Cross-sectional	Gifts	Positive attitude towards PSR interactions
43	Siddiqui et al., 2014	Pakistan	Not reported	Questionnaires of 352 medical students	Cross-sectional	Interaction with representative	Positive attitude towards PSR interaction
55	Workneh BD et al., 2016	Ethiopia	February-March 2015	Survey of 90 physicians from public and private health facilities	Cross-sectional	Interaction with representative, gifts	Positive attitude towards industry, impact on prescribing behavior; Nearly half of the physicians reported that their prescribing decisions were influenced by PSR
57	Khan N et al., 2016	Pakistan	Not reported	Questionnaires in 472 physicians	Cross-sectional	Interaction with representative, gifts	Positive attitude towards PSR interaction
58	Saito S et al. 2010	Japan	January-March 2008	1417 physicians working in internal medicine, general surgery, orthopedic surgery, pediatrics, obstetrics-gynecology, psychiatry, and ophthalmology	National Survey	Interaction with industry, receipt of gifts, funds, CME, samples	Positive attitude towards PSR and gifts, value information from PSR, interactions higher with physicians who prefer to prescribe brand names
59	Ziegler MG et al. 1995	USA	1993	27 physicians working in public and	Survey	Accuracy of information provided by PSRs about	Incorrect information often provided by

				private hospitals		drugs	speakers goes unnoticed by physicians
60	Lurie N et al., 1990	USA	Not reported	240 internal medicine faculty physicians in academic medical centers	Survey	Effect of interaction with PSR, free meals, honoraria and research support	Impact on prescribing behavior and formulary change requests
62	DeJong C et al., 2016	USA	August-September 2013	279.669 physicians who wrote Medicare prescriptions in any of 4 drug classes: statins, cardioselective β-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ACE inhibitors and ARBs), and selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs) Physicians	Cross-sectional	Industry sponsored meals	Receipt of industry-sponsored meals was associated with an increased rate of brand name prescription.
63	Yeh JS et al., 2016	USA	2011	All licensed Massachusetts physicians who wrote prescriptions for statins paid for	Cross-sectional	Effect of industry payment on prescription of branded drugs for cholesterol control	Payment for meals and educational programs increased prescription of brand name

				under the Medicare drug benefit in 2011 (n=2444)			statins.
65	Bowman MA et al., 1988	USA	Not reported	121 physician attendees	Self report survey	Effect of CME on prescribing behavior	Sponsoring company's drugs were favored during prescription
66	Fischer MA et al., 2009	USA	November 2006-March 2007	Multi-disciplinary focus groups with 61 physicians	Survey	Effect of industry marketing strategies on prescription and cognitive dissonance of physicians	Most participants reported no PSR impact on their prescribing, value to have ability to evaluate information of PSRs
67	Chimonas S et al., 2007	USA	June 2004	Six focus groups in 32 academic and community physicians	Survey	PSR interactions	Positive attitude towards PSR interaction
72	Yeh JS et al., 2014	USA	Not reported	1610 US medical students	Cross-sectional	Interaction with representative, gifts, lunches	Policies separating students from representatives reduced number of interactions
73	Larkin I et al., 2014	USA	January 2006-June 2009	Pediatricians, child & adolescent psychiatrists in five medical centers	Survey	Interaction with PSR	Anti detailing policies reduced the prescription of off-label antidepressants and anti psychotics for children
74	Esmaily HM et al., 2010	Iran	Not reported	112 general physicians were randomized in two groups: 1) outcome-	Randomized trial	Effect of outcome and retinal prescribing	Rational prescribing improved in some of the important outcome-based

				based educational intervention for rational prescribing and 2) concurrent CME program in the field of rational prescribing			indicators. No difference between two arms of the study
76	Parikh K et al., 2016	USA	2014	descriptive, cross-sectional analysis of Open Payments data and 9 638 825 payments to physicians and pediatricians from January 1 to December 31, 2014	Cross-sectional	Comparison of PSR interactions between pediatricians and other specialists; among subspecialities of pediatrics.	Pediatricians get fewer gifts from PSR than internists. There is variation among sub specialities for extent of interaction.
78	Chressanthis GA et al. 2012	USA	Not reported	Clinical decisions of 72,114 physicians were statistically analyzed using prescription data	Survey	Effect of restricting PSRs on clinical practice and knowledge	Restricting PSRs affected information flow about drugs, both negative and positive.

. We excluded 2000 records as they were not relevant (n = 1641), not original research (n=269), about medical students (n=4) and non-medical (e.g. ecological, econometric; n=86).

Characteristics of included studies

The identified studies were published between 1992 and August 2016. Most of the studies included were cross-sectional studies[1,9-13,19,21,22,31-55]. Only two studies were cohort studies[56, 57], three were randomized trials[58-60] and one study was a case-control study[61].

Extent of interactions between physicians and the pharmaceutical industry

We found that PSR interactions are a regular feature in the daily lives of physicians across the world [9-11,13,42,50]. Most of the attending physicians and residents have at least one interaction

with industry representatives per month [10,21,22,36,42]. The frequency of interactions or gifts offered and accepted varies with private versus public hospital setting and the position of the physicians in the medical hierarchy [10,13,31,38,42,43,50,58,62]. Junior residents received twice as much free drug samples from PSR interactions than senior residents [10]. PSR interactions were significantly higher at the beginning of residency[13]. The majority of program directors of internal medicine residencies in the USA allowed PSRs to meet with residents during working hours and permitted PSR sponsorship of conferences[40]. Attending physicians and physician specialists had more PSR interactions and received higher numbers of medical samples and promotional material than residents[9,42]. Participants working in private practice alone or in both sectors were more likely to receive gifts than physicians working in the public sector [38,42,50].. Most common gifts received were medical samples[9,21,22,31,36,37,42,63], promotional material[9,34,42] invitations for dinners[9], invitations for CMEs[22,34], scientific journals[34] and free lunches[21,37].

Perspectives of physicians towards PSR interactions

We found that physicians have a positive attitude towards PSRs[1, 13, 19, 20, 22, 31, 32, 40, 49, 58, 64] Physicians perceived PSRs as important sources of education and funding[10, 22, 32, 43, 45, 46]; while some studies reporting skeptical attitudes about the contribution of PSRs towards teaching and education[21, 36, 39, 40, 49]. Conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models, and free drug samples were considered as appropriate gifts[19, 39, 51, 58]. Most of the physicians considered pharmaceutical information provided by PSRs, industry sponsored conferences and CME events as important instruments for enhancing their scientific knowledge[22, 32, 45, 46]. Compared to senior residents, significantly more junior residents felt that pharmaceutical representatives have a valuable teaching role [10].

. Most studies found that physicians do not believe that PSR interactions impact their prescribing behavoir,[1, 9-13, 65, 66], while other studies found that there was some extent of influence[21, 22, 34, 36, 37, 39, 43]. In addition, physicians considered their colleagues more susceptible than themselves to PSR marketing strategies[1, 20, 21, 37, 43]. There was a strong correlation between the amount of gifts and the belief that PSR interactions did not influence their prescribing behavior [10].

Gifts

We found that better scores on knowledge and attitudes were significantly associated with fewer interactions with representatives and their gifts[19]. Conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models, and free drug samples were considered as appropriate gifts[19, 39, 51, 58.] Most of the physicians considered themselves immune to the influence of gifts[1, 10, 32, 33, 35, 37, 43, 59.] Most common gifts received were medical samples[9, 21, 22, 31, 36, 37, 42-44, 47], promotional material[9, 34, 42, 67] invitations for dinners[9] and scientific journals[34]

Drug samples

Most of the physicians who accepted drug samples had a positive attitude towards the pharmaceutical representatives[9, 21, 22, 31, 36, 37, 42, 43]. Accepting samples lead to higher branded drug prescription rather than generic prescribing [22,47].

Pharmaceutical representative speakers

Sponsored lectures/symposia of pharmaceutical companies influenced behavior of the attendees leading to the attendees prescribing more drugs from the sponsoring companies without sufficient evidence supporting superiority of those drugs[56,57]. The majority of attending physicians failed to identify inaccurate information about the company drug[18].

Honoraria and Research Funding

Physicians who received money to attend pharmaceutical symposia or to perform research requested formulary addition of the company's drug more often than other physicians, This association was independent of many confounding factors[61] (Table 2). Brief encounters with PSRs and receipt of honoraria or research support were predictors of faculty requested change in hospital formulary[68].

Conference travel

Pharmaceutical company sponsored conference travels to touristic locations have quantifiable impact on the prescribing rational of attendees. A significant increase (three times) in the prescribing rate of two company drugs was observed after the physicians attended a company sponsored symposium with all their expenses covered. Despite this significant difference in the prescribing patterns, physicians insisted there was no impact on their prescribing behaviour.[57]

Industry paid lunches

Most physicians received invitations for dinners[9] and free lunches[10, 21, 35, 43] . Clerks, interns and junior residents attended more company sponsored lunches than senior residents [10]. Pharmaceutical companies also sponsored departmental lunches during journal clubs[39]. There was no significant association between attending industry paid lunches[37] and dinners[9] and formulary request for that company's drug (Table 2).

#	Attitudes	Prescribing behavior	Knowledge	Formulary requests	Quality of Evidence (GRADE)
Gifts	Receiving higher number of gifts associated with belief that PRs 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 with PRS	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, 69].

CME sponsorship

Physicians who attended company sponsored CME events had more positive attitudes towards and inclination to prescribe the branded drugs[28, 34, 43, 67, 70-72]. We found that physicians who refused CME sponsorship were seen to prescribe higher proportion of generics and lower expenditure medicines when compared to physicians who attended CMEs[22].

Discussion

We report that there is widespread interaction between the pharmaceutical industry and physicians[9-11, 13, 42, 50]. Interactions are in the form of personal communications, free gifts such as drug samples, sponsored meals, sponsored conference travel, funding for research and CMEs and honoraria[9, 21, 22, 31, 36, 42]. The frequency of these interactions is comparable between residents and physicians[10, 21, 22, 36, 42]. However, the amount and type of gifts vary with the position of the physician in medical hierarchy, specialization and location of practice[10, 13, 31, 38, 42, 43, 50, 58, 62]. In general, trainees (residents, interns) are treated with more drug samples, stationery items and free meals than senior physicians[10,13]. Senior physicians usually avail of sponsored conferences/ trips, research funding, honoraria and CME events. The extent of these interactions varies with academic versus non-academic institutions: non-academic hospitals record more interactions than others[31, 38, 42, 50, 55]. The majority of the physicians do not believe that they are affected by PSR interactions[1, 10, 32, 33, 35, 37, 43, 59] . However, a sizeable percentage in various surveys responded in the affirmative when asked whether they thought that their peers are vulnerable[1, 20, 21, 37, 43].

We observe that there is a positive correlation between acceptance of gifts and physicians' urge to reciprocate favorably towards the benefactor[12,22,47, 73, 74] Considering that physicians have a social contract with society at large to provide unbiased and altruistic service, this is an alarming observation. In 2005 a joint report by the WHO and Health Action International (HAI) reported on interventions to counter promotional activities.[75] The evidence presented in that report was not eligible for our systematic review, mostly because it related to interventions on students or residents. Nevertheless, the findings suggested that interventions such as industry self-regulation and guidelines for sales representatives are not effective, while education about drug promotion might influence physician attitudes[76-78].

Policies and educational intervention

The relationship of physicians with patients is of a fiduciary nature. Hence activities that might affect that relationship by altering physicians' clinical behavior are not acceptable. Physician-pharmaceutical industry and PSR interactions may put the trust of patients in physicians at risk. Interaction with pharmaceutical industry and PSRs begins early in the physicians' career. Trainees are exposed to pharmaceutical industry marketing and promotional techniques from the initial years of their medical education, which impact their prescribing behavior in future. Overall, trainees, i.e., residents and interns, are more vulnerable to pharmaceutical industry and PSR interactions than senior physicians[11, 41, 62] Physicians are susceptible to pharmaceutical industry and PSR interactions, which influences their clinical decision-making leading to greater prescriptions of branded drugs over low cost generic medicines and increasing healthcare cost[22, 47, 52, 53, 69] Therefore, there is need to institute and implement stringent policies curtailing physician-pharmaceutical industry and PSR relationships, as well as educational programs to increase awareness. Previous reports have indicated that implementing policies and conducting educational programs are effective in increasing awareness of physician's attitudes towards pharmaceutical industry and PSR interactions[54, 59, 60, 76, 79-83]

Strengths and Limitations of the study

A major strength of this study is that is a large up-to-date systematic review of studies exploring the effects of physician and pharmaceutical industry representative interactions and residents in different settings (e.g. academic, primary care). Another strength of this study is the use of Cochrane and GRADE methodologies for conducting a review and assessing the quality of the studies. Moreover, we performed an extensive search in 3 databases and the

grey literature. Some of the limitations of this review are related to the included studies, as some did not provide evidence for the significance of their findings or had varying study designs and outcomes, which made it impossible to conduct a meta-analysis. Also, the included studies were subject to risk of bias related to the lack of validity of outcome measurement, and inadequate handling of significant potential confounders.

Future implications

Pharmaceutical industry and PSR interactions compromise the objectivity of the physicians. Educating physicians and increasing regulation of pharmaceutical industry and PSR interactions may lower the likelihood of prescribing new non-superior industry drugs and irrational prescription behavior. Further studies are required to evaluate the impact of pharmaceutical industry and PSR interactions on physicians over time and the benefits of various intervention based education programs on the clinical and ethical behavior of the physicians.

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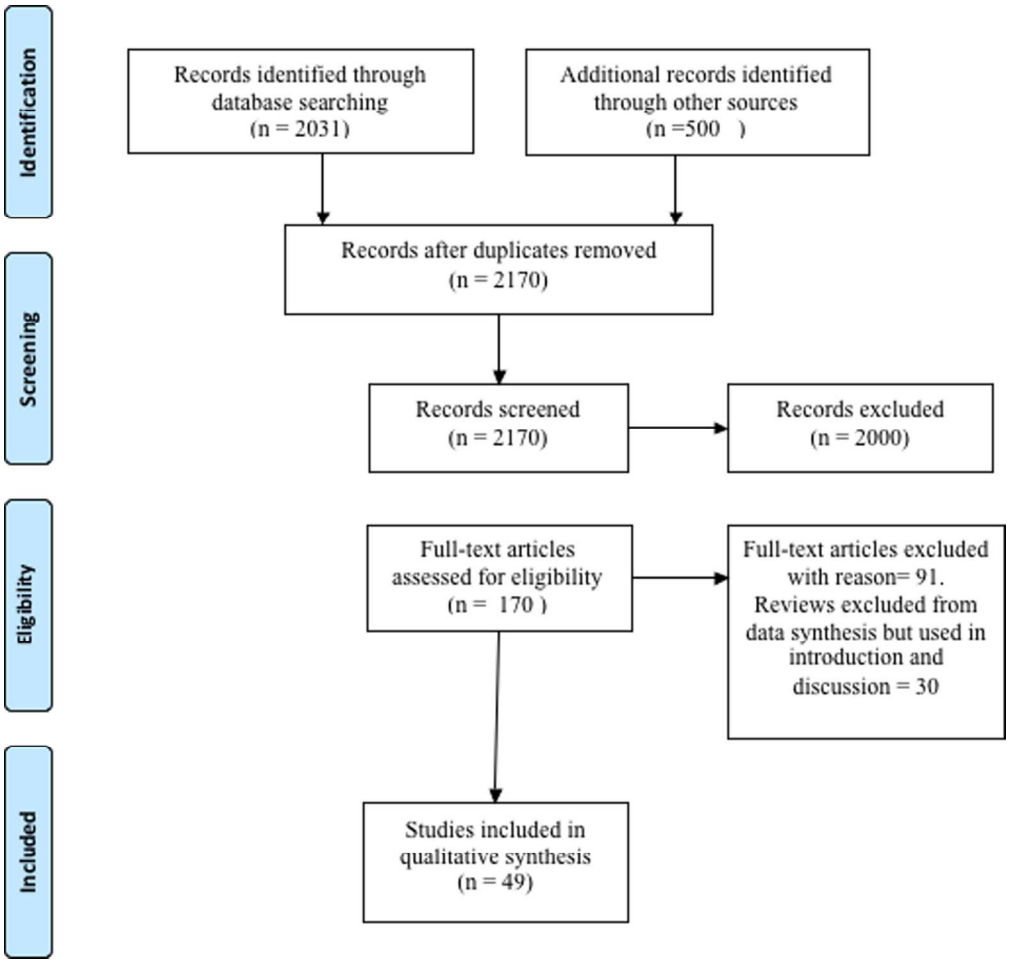
Legends

Figure 1: PRISMA flow diagram showing search strategy and included studies

Table 1: Characteristics of included studies

Table 2: Impact of physician-pharmaceutical industry interaction on physician

Supplementary information file: Search strategy



Flow diagram of study selection.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3/4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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For more information, visit: **www.prisma-statement.org**.

Search strategy for PubMed search engine of Medline

In an attempt to find all related literature on the topic, studies related to physician-pharmaceutical representative interactions that affect the prescribing behavior of the physicians were identified through computerized searches using, but not limited to, the following subject headings and text words in PubMed from 1992 to 2016.

1. Physician interactions with pharmaceutical industry
2. Physician attitude towards pharmaceutical representatives
3. Behavior of physicians towards pharmaceutical representatives
4. Gifts AND physician AND pharmaceutical representatives
5. Honoraria AND physician AND pharmaceutical representatives
6. Continuing medical education AND physician AND pharmaceutical representatives
7. Research funding AND physician AND pharmaceutical representatives
8. Conference travel AND physician AND pharmaceutical representatives
9. Industry sponsored meals AND physician behavior