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Interventions targeting physicians' interaction with pharmaceutical companies: A systematic review

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Interventions targeting physicians' interaction with pharmaceutical companies: A systematic review

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ABSTRACT

Background

Pharmaceutical company representatives likely influence the prescribing habits and professional behavior of physicians. The objective of this study was to systematically review the effects of interventions targeting physicians' interactions with pharmaceutical companies.

Methods

We used the Cochrane approach to systematic review. The search strategy included an electronic search of MEDLINE and EMBASE. Two reviewers completed in duplicate and independently study selection, data abstraction, and assessment of risk of bias. We assessed the quality of evidence by outcome using the GRADE methodology.

Results

Of 10,189 identified citations, one randomized clinical trial and three observational studies met the eligibility criteria. The RCT provided moderate quality evidence of no effect of a "collaborative approach" between the pharmaceutical industry and the health authority. The three observational studies provided low quality evidence suggesting a positive effect of policies aiming to reduce interaction between physicians and the pharmaceutical companies (in the form of free samples, promotional material, and meeting with pharmaceutical company representatives) on prescription behavior.

Conclusion

Available evidence suggests a potential impact of policies aiming to reduce interaction between physicians and the pharmaceutical companies on physicians' prescription behavior.

ARTICLE SUMMARY: STRENGHTHS AND LIMITATIONS OF THIS STUDY

Strengths

- We conducted the systematic review using the Cochrane Collaboration methodology.
- This is the first systematic review to focus on interventions targeting practicing physicians.

Limitations:

- We identified a limited number of studies to allow strong conclusions.
- The included studies suffered from risk of bias related mostly to the lack of validity of outcome measurement, and the inadequate handling of significant potential confounders.

INTRODUCTION

Physicians may benefit from the relationship with pharmaceutical industry through access to information on new medications and products. However, the direct financial rewards provided to them could be used to persuade them to prescribe newer and more expensive drugs to patients. [1]

Drug industry also promotes its products through supporting continuing medical education. There is also a concern that by paying for the doctors' continuing education, drug companies makes sure physicians learn what is important for the corporate bottom line.[2]

As a result to these concerns, legislators have tried to improve the transparency of the relationships between doctors and drug companies. [3] For example, the Physician Payments Sunshine Act (Sunshine Act) in the United States requires manufacturers of drugs, medical devices and biologicals participating in federal health care programs to report certain payments and items of value given to physicians and teaching hospitals.[4]

There have been also training programs to help restrict physicians' interactions with the pharmaceutical companies.[5] The purpose of these programs is to help physicians better understand the conflicts of interest associated with the acceptance of gifts and other financial incentives and their potential effect on patient care.

The objective of this study was to systematically review the effects of interventions targeting physicians' interactions with pharmaceutical companies.

METHODS

Protocol and registration

Protocol was not registered.

Eligibility criteria

The eligibility criteria were:

- Types of studies: observational studies (e.g., cohort), non-randomized controlled trials, and randomized controlled trails.
- Types of participants: practicing physicians; we did not consider medical students, physicians in training, or other health professionals.
- Types of interventions: legislative, educational, policy, or other interventions targeting the interaction between physicians and drug representatives;
- Types of outcomes: knowledge of physicians (e.g., about the potential effect of interactions on physician prescribing behavior); attitude of physicians (e.g. toward the usefulness of

information from pharmaceutical company representatives); behavior of physicians (e.g., prescription behavior, the rate of contact with pharmaceutical company representatives).

We did not exclude studies based on date of publication, but excluded studies not published in English.

Search Strategy

We designed the search strategy with the help of a medical librarian (Appendix 1). The strategy included searching MEDLINE and EMBASE electronic databases using the OVID interface in September 2012. The search combined terms for physicians, and pharmaceutical, and included both free text words and medical subject heading. We did not use any search filter. The appendix provides the full details of the search strategies. Additional search strategies included search of the grey literature (theses and dissertations). Also, we reviewed the references lists of included and relevant papers.

Selection of studies

Two reviewers screened in duplicate and independently the titles and abstracts of identified citations for potential eligibility. We obtained the full text for citations judged as potentially eligible by at least one of the 2 reviewers. The two reviewers then screened in duplicate and independently the full texts for eligibility. They used a standardized and pilot tested screening form and resolved disagreement by discussion.

Data collection

Two reviewers abstracted in duplicate and independently data from eligible studies. They used a standardized and pilot tested screening form and detailed written instructions. They resolved disagreement by discussion. We calculated the agreement between the two authors for the assessment of trial eligibility using kappa statistic. The data abstracted included the type of study; the funding source; the characteristics of the population, exposure, and control; the outcomes assessed; and statistical data.

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. According to recommendations outlined in the Cochrane Handbook, we used the following criteria for assessing the risk of bias in randomized studies:

- Inadequate sequence generation;
- Inadequate allocation concealment;
- Lack of blinding of participants, providers, data collectors, outcome adjudicators, and data analysts
- Incompleteness of outcome data.
- Selective outcome reporting, and other bias.

We used the following criteria for assessing the risk of bias in non-randomized studies:

- Failure to develop and apply appropriate eligibility criteria (e.g., under- or over-matching in case-control studies, selection of exposed and unexposed in cohort studies from different populations)
- Flawed measurement of both exposure and outcome (e.g., differences in measurement of

exposure such as recall bias in case-control studies, differential surveillance for outcome in exposed and unexposed in cohort studies

- Failure to adequately control confounding (e.g., failure to accurately measure all known prognostic factors, failure to match for prognostic factors and/or adjustment in statistical analysis
- Incomplete follow-up

We graded each potential source of bias 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 in a narrative way.

RESULTS

Description of included studies

Figure 1 shows the study flow. Of the 10,189 identified articles, three observational studies and one randomized trial met our inclusion criteria. The value of kappa statistic for full text screening was 0.893, reflecting high levels of agreement.

Tables 1 and 2 show the characteristics of the included studies. These studies were conducted in Warwickshire in the United Kingdom, central Oregon in the United States, Brisbane in Australia, and Southeastern of the United States. Three studies evaluated the effects of the implementation

of new legislations and regulatory policies [6-8] while one study evaluated the effects of various educational interventions. [9] These studies assessed the impact of interventions on physician knowledge, attitudes and behavior. The sample sizes in these studies also varied from 14 to 79.

Table 3 shows the assessment of the risk of bias in the one included RCT. The risk of bias was judged to be either low or unclear for the different criteria assessed. [9] Table 4 shows the assessment of the risk of bias in the three included observational studies. [6-8]We judged the risk of bias associated with the exposure measurement and the completeness of data as low for all included studies. We judged the risk of bias as either low or unclear for the remaining methodological features, except for confounding which we judged as high risk for one study. [7]

Effects of implementing new policies

As mentioned previously, one trial and three observational studies evaluated the effects of program or organizational policies that limit contact between physicians and pharmaceutical company representatives.

Freemantle et al, [9] conducted a randomized controlled trial where both the intervention and the control groups received practice guidelines, routine marketing act, and a routine health authority advice. In addition, the interventional group received post-graduate educational allowance accreditation and a letter from the pharmaceutical advisor asking the practice to “agree to see the representative preceded approaches by company representatives to specific practices”. The objective was to assess the “additional benefits from a collaborative approach” between the pharmaceutical industry and the health authority. Prescribing in both groups “moved towards that

recommended by the guidelines". However, the proportion of prescriptions in line with the guidelines and the overall cost were not different between the two groups.

Boltri et al. [6] conducted a retrospective cohort study of a new policy prohibiting drug samples distribution (mainly hypertensive drugs). Participants included 24 family practice residents and 8 clinical attending physicians at an outpatient clinic in the southeastern United States. At six months after the new policy implementation, prescription of first-line medication increased from 38% to 61% (odds ratio (OR)=2.73, 95% CI=1.29, 5.76)

Spurling et al. [7] examined a cohort of 14 participants, 3 months prior and 9 months after the implementation of a new policy that included: reception staff not making appointments for pharmaceutical sales representatives nor accepting promotional material; pharmaceutical sales representatives not accessing sample cupboards; and general practitioners wishing to see pharmaceutical sales representatives may do so outside consulting hours.

The investigators found that the number of overall promotional material were reduced by 32% and 21% at 3 and 9 months respectively post-intervention compared to pre-intervention. The number of samples was reduced by 59%, and 70% at 3 and 9 months respectively post-intervention compared to pre-intervention. The number of prescriptions per patient encounter fell from 0.99 pre-intervention to 0.92 and 0.54 at 3 and 9 months post-intervention respectively. The number of generic prescriptions increased from 4% pre-intervention to 8.6% and 8.1% after 3 and 9 months post-intervention, respectively.

Hartung et al. [8] evaluated the effects of the implementation of new policies applied by the Madras Medical Group family practice clinics. The policies included discontinuing seeing pharmaceutical representatives and stopping acceptance and distributing drug samples. The control group consisted of a regionally discrete sample of Medicaid enrollees who were not also enrolled in Medicare. The analysis used segmented linear regression models to compare 92,223 and 178,028 pharmacy claims from the intervention and control groups covering 18 months before and 18 months after policy implementation. In aggregate, use of "promoted agents" decreased by 1.4% whiles the use of "non-promoted branded agents" increased by 3.0%. However, the results varied by the class of drug. Interestingly, the investigators found that the average prescription drug cost increased significantly (by USD 5.2) immediately after policy implementation

Discussion

In summary, our systematic review identified one RCT [9] and three observational studies. [6 -8] The RCT found no effect of a "collaborative approach" between the pharmaceutical industry and the health authority. The three observational studies found a positive effect on prescription behavior of clinic policies aiming to reduce interaction between physicians and the pharmaceutical companies (in the form of free samples, promotional material, and meeting with pharmaceutical company representatives).

A major strength of this study is the use of Cochrane methodology for conducting the systematic review. In addition, this is the first systematic review to focus on practicing physicians. Some of the limitations of this review relate to those of the included studies. Indeed, we identified a limited number of studies to allow strong conclusions. Also, the included studies suffered from risk of bias

related to the lack of validity of outcome measurement, and the inadequate handling of significant potential confounders.

The quality of evidence from the RCT was judged to be moderate due to imprecision (only 79 participants). The quality of evidence from observational studies was judged to be low due to study design. Indeed, overall risk of bias was judged as low, and we did not find any evidence of inconsistency, imprecision, indirectness or publication bias warranting further downgrading.

We identified only one other systematic review of the literature addressing the same question but with residents instead of practicing physicians.[5] The review identified 12 eligible studies, seven before-after studies and three controlled trials. The findings suggested that well-designed seminars, role-playing, and focused curricula could affect trainee attitudes and behavior. However, it was not clear whether these effects were sustainable long-term.

Implications for practice

Based on the evidence, health administrators aiming to reduce the negative impact of physicians' interaction with pharmaceutical companies may not want to spend their resources on "collaborative approaches" between pharmaceutical industry and the health authority. They are more likely to benefit from implementing policies restricting free samples, industry supplied promotional materials, and meeting with pharmaceutical company representatives.

Implications for research

Future studies should address the methodological limitations of the available evidence. This includes conducting well-designed randomized trials. Future observational studies should aim for

proper assessment of the exposure, controlling for all confounders, and minimizing missing data. Future studies should also consider other types of interventions, including educational and legislative one.

TABLES AND FIGURES

Table 1: Characteristics of included RCT

Study Name	Study Design	Participants, setting	Exposure	Control	Outcomes	Notes
Freemantle, 2000 Funding by Warwickshire Health Authority	• Randomized controlled trial	• All 79 cardiovascular practices in Warwickshire participated in the trial.	• 40 practices who received, in addition to what the control group received: • Letter from the chief executive of the health authority • Postgraduate educational allowance accreditation • A letter from the pharmaceutical advisor	• 39 practices who received: • Practice guidelines • Routine marketing act • Routine health authority advice	• Proportion of prescriptions in line with the guidelines (behavior) • Prescribing costs	• Time frame: October 1997 and April 1998.

Table 2: Characteristics of included observational studies

Study Name and funding	Study Design	Participants, setting	Exposed group	Control group	Outcomes	Notes
Boltri 2002 Funding by the Health Resources and Services Administration	• Retrospective cohort • Charts from two time periods were reviewed for a diagnosis of hypertension	• 24 family practice residents and 8 clinical attending physicians faculty at the outpatient clinic of a family practice residency program in the southeastern United States.	• 507 hypertensive patients during "Period 2": January and February 1998 after the policy prohibiting samples distribution was implemented in august 1997	• 422 hypertensive patients during "Period 1": January and February1997before the policy prohibiting samples distribution was implemented.	• Effect of policy on prescription of first line hypertension drugs versus prescription of second-line drugs by all physicians (by JNC VI)	• Data collection of the outcome was based on the medical reports of all hypertensive patients during the two study periods.
Spurling, 2007 Funding not reported	• Prospective cohort	• 13 out of the 14 (7 part-time general practitioners (GPs), 3 practice nurses, 3 regular reception staff, 1 practice manager) participated • Inala Health Centre General Practice in Brisbane, Australia	-Policy of reduced access to pharmaceutical sales representatives including: reception staff not to make appointments for representatives or accept promotional material; representatives cannot access sample cupboards; GPs wishing to see representatives	• Pre policy	• Number of prescription per patient (behavior) • Number of promotional materials (no further details provided) • Number of samples in the drug cupboard and time booked for pharmaceutical sales representatives (actual implementation of the policy •	• Timeframe:2004 • The policy was evaluated 3months pre policy and 9 months post policy • Data collected through audit and staff survey

			may do so outside consulting hours.			
Hartung, 2010 Funding in part by an American Academy of Family Physicians Foundation Research Stimulation Grant	• Segmented linear regression models using locally obtained pharmacy claims.	• The Madras Medical Group, a family practice clinic employing 5 physicians and 1 physician assistant;	• After the implementation of a policy restricting access of pharmaceutical sales representatives to the clinic was implemented	• Before the implementation of the a policy • Oregon Medicaid pharmacy claims were used to control for secular prescribing changes.	• Percentage of branded drug use (behavior) • Percentage of promoted drug use (behavior) • Average prescription costs (cost)	• Time Frame: April 1, 2004, to September 31, 2007. • In January 2006 the Medicare Part D program was implemented

Table 3: Risk of bias in included RCT

Study Name	Sequence generation	Allocation concealment	Blinding (participants, data collectors, outcome adjudicators)	Completeness of outcome data	Completeness of outcome reporting
Freemantle, 2000	Low risk "Practices were randomized to intervention or control using computer generated random numbers in a stratified scheme"	Unclear risk Not reported	Unclear risk Not reported	Low risk No missing data reported	Low risk No evidence of selective outcome reporting

Table 4: Risk of bias in included observational studies

Study Name	Developing and applying appropriate eligibility criteria	Measurement of exposure	Measurement of outcome	Controlling for confounding	Completeness of data
Boltri 2002	Low risk Physicians and residents in the control and exposed groups are of the same pool	Low risk Policy applied across the clinic	Low risk Data collection was based on medical records, and done by research assistant blinded to study design and hypothesis	Low risk "Logistic regression was then performed to adjust the odds ratio for the relation of physician type, prescribing patterns, and time."	Low risk No missing data reported
Spurling, 2007	Low risk Diaries chosen at random for a 1-month period .A random week was chosen to audit doctors' prescribing.	Low risk Policy applied across the clinic	Unclear risk Not clear whether the survey instrument was validated	High risk According to the authors, the possibility of confounding cannot be ruled out	Low risk. All except one returned the completed questionnaire
Hartung, 2010	Unclear risk	Low risk Policy applied across the clinic	Unclear risk Use of claim data; however validity of the data not described	Low risk They include "a contemporaneous control group of patients or clinicians also experiencing this potential confounder." (confounding resulting from secular changes in prescribing).	Low risk 'Although it is possible that some prescriptions would not have been captured by using data from only one pharmacy, it seems unlikely that this subset would have introduced any systematic bias or loss of generalizability."

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Contributions of authors

Concept and design: EAA, LA, KM

Study selection: LA, LK, HN, HB

Data collection: LA, LK

Data analysis and interpretation: EAA, LA, LK, HB, KM

Drafting of the manuscript: EAA, LA

All authors reviewed and approved the submitted version of the manuscript.

COMPETING INTERESTS

No competing interests to declare.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

DATA SHARING STATEMENT

There is no additional data available.

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APPENDICIES

Appendix 1: Search strategy

Medline 1946 to October Week 2 2012

Conflict of Interest.mp.or "Conflict of Interest"/

Drug Industry/

Gift Giving/

detailman.mp.

commercial information.mp.

((drug or pharma*) adj3 (industry or firm* or manufacture* or compan*)).mp.

physician*.mp.

doctor*.mp.

Physicians/

primary care.mp.

EmBASE 1980 to 2012 Week 41

Conflict of Interest.mp.or "Conflict of Interest"/

Drug Industry/

Gift Giving/

detailman.mp.

commercial information.mp.

((drug or pharma*) adj3 (industry or firm* or manufacture* or compan*)).mp.

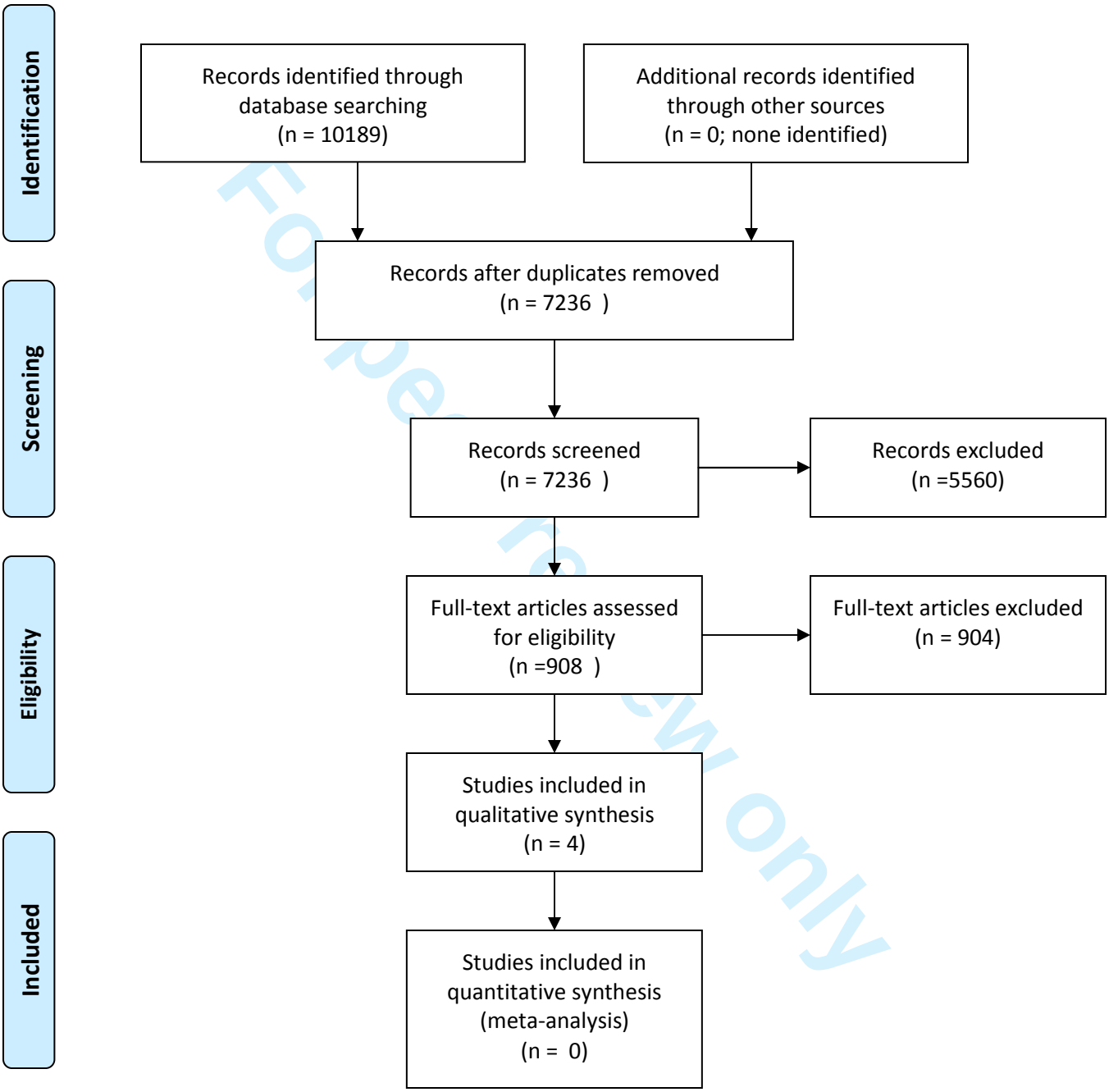
physician*.mp.

doctor*.mp.

Physician/

primary care.mp.

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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

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, 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	5
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.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, 6
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).	6
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.	6, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
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.	8

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).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A: Not Applicable
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.	8
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.	8, 9
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).	9
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.	9, 10, 11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A: Not Applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16, 17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
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).	10, 11, 12
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).	3, 10, 11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11, 12
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.	18

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

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Primary Subject Heading:	Health services research
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Legislative, educational, policy, and other interventions targeting physicians' interaction with pharmaceutical companies: A systematic review

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ABSTRACT

Background: Pharmaceutical company representatives likely influence the prescribing habits and professional behavior of physicians.

Objective: The objective of this study was to systematically review the effects of interventions targeting practicing physicians' interactions with pharmaceutical companies.

Eligibility criteria: we included observational, non-randomized controlled trials, and randomized controlled trials evaluating legislative, educational, policy, or other interventions targeting the interactions between physicians and pharmaceutical companies

Data sources: The search strategy included an electronic search of MEDLINE and EMBASE. Two reviewers completed in duplicate and independently study selection, data abstraction, and assessment of risk of bias.

Appraisal and synthesis methods: We assessed the risk of bias in each included study. We summarized the findings narratively because the nature of the data did not allow conducting a meta-analysis. We assessed the quality of evidence by outcome using the GRADE methodology.

Results: Of 11,189 identified citations, one randomized clinical trial and three observational studies met the eligibility criteria. All four studies specifically targeted one type of interaction with pharmaceutical companies, i.e., interactions with drug representatives. The RCT provided moderate quality evidence of no effect of a "collaborative approach" between the pharmaceutical industry and the health authority. The three observational studies provided low quality evidence suggesting a positive effect of policies aiming to reduce interaction between physicians and the pharmaceutical companies (in the form of restricting free samples, promotional material, and meeting with pharmaceutical company representatives) on prescription behavior.

Limitations: We identified a limited number of studies to allow strong conclusions.

Conclusion: Available evidence suggests a potential impact of policies aiming to reduce interaction between physicians and drug representatives on physicians' prescription behavior. We identified no evidence about interventions affecting other types of interaction with pharmaceutical companies.

Article summary

Article focus

- To systematically review the effects of interventions targeting practicing physicians' interactions with pharmaceutical companies

Key messages

- There is a potential impact of policies aiming to reduce interaction between physicians and drug representatives on physicians' prescription behavior
- Potentially effective policies include: restricting free samples, promotional material, and meeting with pharmaceutical company representatives

Strengths and limitations of this study:

- We followed Cochrane methodology for conducting this systematic review.
- This is the first systematic review to focus on practicing physicians.
- We identified a limited number of studies to allow strong conclusions.

INTRODUCTION

Physicians may benefit from the relationship with pharmaceutical industry through access to information on new medications and products. However, the direct financial rewards provided to them could be used to persuade them to prescribe newer and more expensive drugs to patients.[1] One industry market study found that physician profiling could increase the uptake of new drugs by 30%.[2] On the other hand, studies conducted in different parts of the world (e.g., Canada, France the United States, Australia and Malaysia) have consistently found that risk and harmful effects of drugs were often missing in presentations by pharmaceutical representatives to doctors.[3]

Similarly, there is a concern that by paying for the doctors' continuing education, drug companies make sure physicians learn what is important for the corporate bottom line.[4] A recent review article on this subject showed that industry-supported educational activities are biased toward the financial supporter's products and that clinicians attending such activities later prescribe these products more often than competing drugs [5]. One study found that pharmaceutical representatives commonly use different types of "influence techniques" when they detail products to medical practitioners.[6]

As a result to these concerns, legislators have tried to improve the transparency of the relationships between doctors and drug companies[3]. For example, the Physician Payments Sunshine Act (Sunshine Act) in the United States requires manufacturers of drugs, medical devices and biologicals participating in federal health care programs to report certain payments and items of value given to physicians and teaching hospitals [7].

There have been also training programs to help restrict physicians' interactions with the pharmaceutical companies including well-designed seminars, role playing, and focused curricula [8].The purpose of these programs is to help physicians better understand the conflicts of interest associated with the acceptance of gifts and other financial incentives and their potential effect on patient care.

While there has been at least one systematic review assessing interventions targeting residents and students interaction with pharmaceutical companies, we are not aware of any such systematic review focusing on practicing physicians.[8] The objective of this study was to systematically review the effects of interventions targeting practicing physicians' interactions with pharmaceutical companies.

METHODS

Eligibility criteria

The eligibility criteria were:

- Types of studies: observational studies (e.g., cohort) comparing an intervention of interest to a comparator (e.g., usual practice), non-randomized controlled trials, and randomized controlled trials.
- Types of participants: practicing physicians. We did not consider medical students, physicians in training, or other health professionals.
- Types of interventions: legislative, educational, policy, or other interventions targeting the interactions between physicians and pharmaceutical companies. Examples of such

interactions include contact with drug representatives, educational talks, and sponsored travel, etc.;

- Types of outcomes: knowledge of physicians (e.g., about the potential effect of interactions on physician prescribing behavior); attitude of physicians (e.g. toward the usefulness of information from pharmaceutical company representatives); behavior of physicians (e.g., prescription behavior, the rate of contact with pharmaceutical company representatives).

We did not exclude studies based on date of publication, but excluded studies not published in English.

Search Strategy

We designed the search strategy with the help of a medical librarian (Appendix 1). The strategy included searching MEDLINE and EMBASE electronic databases using the OVID interface in April 2014. The search combined terms for physicians, and pharmaceutical, and included both free text words and medical subject heading. We did not use any search filter. The appendix provides the full details of the search strategies. Additional search strategies included search of the grey literature (theses and dissertations). Also, we reviewed the references lists of included and relevant papers.

Selection of studies

Two reviewers independently screened the titles and abstracts of identified citations for potential eligibility. We obtained the full text for citations judged as potentially eligible by at least one of the 2 reviewers. The two reviewers then independently screened the full texts for eligibility. They used a standardized and pilot tested screening form and resolved disagreement by discussion.

Data collection

Two reviewers independently abstracted data from eligible studies. They used a standardized and pilot tested screening form and detailed written instructions. They resolved disagreement by discussion. The data abstracted included the type of study; the funding source; the characteristics of the population, exposure, and control; the outcomes assessed; and statistical data.

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. According to recommendations outlined in the Cochrane Handbook, we used the following criteria for assessing the risk of bias in randomized studies:

- Inadequate sequence generation;
- Inadequate allocation concealment;
- Lack of blinding of participants, providers, data collectors, outcome adjudicators, and data analysts
- Incompleteness of outcome data.
- Selective outcome reporting, and other bias.

We used the following criteria for assessing the risk of bias in non-randomized studies:

- Failure to develop and apply appropriate eligibility criteria (e.g., under- or over-matching in case-control studies, selection of exposed and unexposed in cohort studies from different populations)
- Flawed measurement of both exposure and outcome (e.g., differences in measurement of

exposure such as recall bias in case-control studies, differential surveillance for outcome in exposed and unexposed in cohort studies

- Failure to adequately control confounding (e.g., failure to accurately measure all known prognostic factors, failure to match for prognostic factors and/or adjustment in statistical analysis
- Incomplete follow-up

We graded each potential source of bias 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 in a narrative way. We assessed the quality of evidence by outcome using the GRADE methodology.[9]

RESULTS

Results of the search Figure 1 shows the study flow. Of the 11,189 identified articles, three observational studies and one randomized trial met our inclusion criteria. We excluded 27 full-text articles for the following reasons: studies assessed the association between interactions with pharmaceutical companies and behaviors (and effects of interventions) (n=15); and studies conducted among students or residents (n=12). The value of kappa statistic for full text screening was 0.893, reflecting high levels of agreement.

Description of included studies

Tables 1 and 2 show the characteristics of the included studies. All these studies assessed interventions that specifically targeted interactions of physicians with drug representatives. We identified no studies of interventions targeting other potential types of interaction with pharmaceutical companies (e.g., educational talks, sponsored travel).

These studies were conducted in Warwickshire in the United Kingdom, central Oregon in the United States, Brisbane in Australia, and Southeastern of the United States. Three studies evaluated the effects of the implementation of new legislations and regulatory policies [10 11] while one study evaluated the effects of various educational interventions[10]] These studies assessed the impact of intervention son physician knowledge, attitudes and behavior. The sample sizes in these studies also varied from 14 to 79.

Table 3 shows the assessment of the risk of bias in the one included RCT. The risk of bias was judged to be either low or unclear for the different criteria assessed [10].Table 4 shows the assessment of the risk of bias in the three included observational studies [7-9]. We judged the risk of bias associated with the exposure measurement and the completeness of data as low for all included studies. We judged the risk of bias as either low or unclear for the remaining methodological features, except for confounding which we judged as high risk for one study [12].

Effects of implementing new policies

As mentioned previously, one trial and three observational studies evaluated the effects of program or organizational policies that limit contact between physicians and pharmaceutical company representatives.

Freemantle et al,[13] conducted a randomized controlled trial to assess the “a collaborative approach” between the pharmaceutical industry and the local health authority. The collaborative approach consisted of post-graduate educational allowance accreditation and a letter from the pharmaceutical advisor asking the practice to agree to see the representative. Both the intervention and the control groups received practice guidelines, routine marketing activity, and a routine Health Authority advice. The authors do not provide further details about the “routine advice”, but the Health Authorities in the United Kingdom apparently enact the directives of the Department of Health, implement its fiscal policy, and run or commission local health services.[14] The specific objective of the intervention was to substitute in primary care a proton inhibitor for an alternative deemed therapeutically equivalent but less costly, based on “evidence based guidelines”. The investigators reported that prescribing in both groups “moved towards that recommended by the guidelines”. However, the proportion of prescriptions in line with the guidelines and the overall cost were not different between the two groups.

Boltri et al. [10]conducted a retrospective cohort study of a new policy prohibiting drug samples distribution (mainly hypertensive drugs). Participants included 24 family practice residents and 8 clinical attending physicians at an outpatient clinic in the southeastern United States. At six months after the new policy implementation, prescription of first-line medication increased from 38% to 61% (odds ratio (OR) =2.73, 95% CI=1.29, 5.76)

Spurling et al examined a cohort of 14 participants, 3 months prior and 9 months after the implementation of a new policy.[12] This policy included: reception staff not making appointments for pharmaceutical sales representatives nor accepting promotional material; pharmaceutical sales

representatives not accessing sample cupboards; and general practitioners wishing to see pharmaceutical sales representatives may do so outside consulting hours.

The investigators found that the number of overall promotional material were reduced by 32% and 21% at 3 and 9 months respectively post-intervention compared to pre-intervention. The number of samples was reduced by 59%, and 70% at 3 and 9 months respectively post-intervention compared to pre-intervention. The number of prescriptions per patient encounter fell from 0.99 pre-intervention to 0.92 and 0.54 at 3 and9 months post-intervention respectively. The number of generic prescriptions increased from 4% pre-intervention to 8.6% and 8.1% after 3 and 9 months post-intervention, respectively.

Hartung et al. [11]evaluated the effects of the implementation of new policies applied by the Madras Medical Group family practice clinics (Ohio, United States). The policies included discontinuing seeing pharmaceutical representatives and stopping acceptance and distributing drug samples. The control group consisted of a regionally discrete sample of the Oregon Medicaid program. Medicaid and Medicare are two governmental programs that provide medical and health-related services to specific groups of people in the United States. The analysis used segmented linear regression models to compare 92,223 and 178,028 pharmacy claims from the intervention and control groups covering 18 months before and 18 months after policy implementation. In aggregate, use of “promoted agents” decreased by 1.4% while the use of “non-promoted branded agents” increased by 3.0%. However, the results varied by the class of drug. Interestingly, the investigators found that the average prescription drug cost increased significantly (by USD 5.2) immediately after policy implementation.

Assessment of the quality of evidence

Following the GRADE methodology, we judged the quality of evidence from the RCT as moderate due to imprecision (only 79 participants). We judged the quality of evidence from observational studies as low due to study design. Indeed, overall risk of bias was judged as low, and we did not find any evidence of inconsistency, imprecision, indirectness or publication bias warranting further downgrading.

Discussion

In summary, our systematic review identified one RCT[13] and three observational studies,[10 11]. All included studies targeted one type of interaction with pharmaceutical companies, i.e., interactions with drug representatives. The RCT found no effect of a "collaborative approach" between the pharmaceutical industry and the health authority. The three observational studies found a positive effect on prescription behavior of clinic policies aiming to reduce interaction between physicians and the pharmaceutical companies (in the form of free samples, promotional material, and meeting with pharmaceutical company representatives). Our systematic review did not identify eligible studies assessing other relevant types of interactions between physicians and pharmaceutical companies, such as educational talks, sponsored travel.

A major strength of this study is the use of Cochrane methodology for conducting the systematic review. In addition, this is the first systematic review to focus on practicing physicians. Some of the limitations of this review relate to those of the included studies. Indeed, we identified a limited number of studies to allow strong conclusions. Also, the included studies suffered from risk of bias related to the lack of validity of outcome measurement, and the inadequate handling of significant potential confounders.

The available evidence does not provide clear answers on why a "collaborative approach" between the pharmaceutical industry and a health authority did not work, while policies restricting certain types of interaction between physicians and the pharmaceutical companies worked. It might be that restriction approaches are easier to implement compared to more complex interventions such collaborative approaches. Also, it might be that the link between the restrictive interventions and the desired outcome is clearer and shorter compared with the collaborative interventions.

The Physician Payment Sunshine Act (PPSA) enacted in 2010 in the United States marks the first Congressional involvement in regulating the disclosure by physicians of payments by pharmaceutical companies. Under this Act, manufacturers of drugs, medical devices and biologicals participating in U.S. federal health care programs 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). The purpose is to prevent undue influence and protect the public interest.[4] The Sunshine Act could be viewed as a systems intervention targeting physicians' interactions with pharmaceutical companies. Although we have not identified at this point any study assessing the impact of this Act on the prescription behavior of physicians, we expect those studies to become available over the next few years.

While acknowledging the importance of regulation, some have called for physicians to take the lead and minimize any undue commercial influence on their profession.[5] Professional organization have a particularly important responsibility, given the relationships between physicians and the pharmaceutical industry may erode social trust in medical professionals.[5]

A 2005 joint report by the World Health Organization (WHO) and the Health Action International (HAI) reported on interventions to counter promotional activities.[15] The evidence presented in that report, although 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 their attitudes. At that time, the report called for research on interventions that could affect doctors' behavior.

We identified only one other systematic review of the literature addressing the same question but with residents and students instead of practicing physicians [8]. The review identified 12 eligible studies, seven before-after studies and three controlled trials. The findings suggested that well-designed seminars, role-playing, and focused curricula could affect trainee attitudes and behavior. However, it was not clear whether these effects were sustainable long-term.

Implications for practice

Based on the evidence, health administrators aiming to reduce the negative impact of physicians' interaction with pharmaceutical companies may not want to spend their resources on "collaborative approaches" between pharmaceutical industry and the health authority. They may possibly benefit from implementing policies restricting free samples, industry supplied promotional materials, and meeting with pharmaceutical company representatives.

However, a potential limitation of implementing restriction policies is creating an "information gap" that has been filled so far by the pharmaceutical representatives (e.g., information on new drugs). Indeed, those representatives provide information to doctors about indications and dosages of

medications to relatively high percentages of physicians [3]. Sales representatives are frequently the only source of information about medicines in developing countries where there may be as many as one representative for every five doctors[16].

As an alternative to complete restriction of interactions, some jurisdictions have attempted to regulate interactions. In Australia, the Australian Pharmaceutical Manufacturers Association has a code of conduct covering sales representatives. Although the code does not state what kind of information sales representatives must provide, it does insist that their presentations be current, accurate and balanced [16].

Implications for research

Future studies should address the methodological limitations of the available evidence. This includes conducting well-designed randomized trials. Future observational studies should aim for proper assessment of the exposure, controlling for all confounders, and minimizing missing data. There is also a need for studies of other types of interventions, (e.g., educational and legislative interventions), as well as target other types of interactions with pharmaceutical companies (e.g., educational talks, sponsored travel). As the Sunshine Act gets implemented, we expect over the next few years the publication of studies assessing its impact on the prescription behavior of physicians.

TABLES

Table 1: Characteristics of included RCT

Study Name	Study Design	Participants, setting	Exposure	Control	Outcomes	Notes
Freemantle, 2000 Funding by Warwickshire Health Authority	• Randomized controlled trial	• All 79 cardiovascular practices in Warwickshire participated in the trial.	• 40 practices who received, in addition to what the control group received: • Letter from the chief executive of the health authority • Postgraduate educational allowance accreditation • A letter from the pharmaceutical advisor	• 39 practices who received: • Practice guidelines • Routine marketing act • Routine health authority advice	• Proportion of prescriptions in line with the guidelines (behavior) • Prescribing costs	• Time frame: October 1997 and April 1998.

Table 2: Characteristics of included observational studies

Study Name and funding	Study Design	Participants, setting	Exposed group	Control group	Outcomes	Notes
Boltri 2002 Funding by the Health Resources and Services Administration	• Retrospective cohort • Charts from two time periods were reviewed for a diagnosis of hypertension	• 24 family practice residents and 8 clinical attending physicians faculty at the outpatient clinic of a family practice residency program in the southeastern United States.	• 507 hypertensive patients during "Period 2": January and February 1998 after the policy prohibiting samples distribution was implemented in august 1997	• 422 hypertensive patients during "Period 1": January and February1997before the policy prohibiting samples distribution was implemented.	• Effect of policy on prescription of first line hypertension drugs versus prescription of second-line drugs by all physicians (by JNC VI)	• Data collection of the outcome was based on the medical reports of all hypertensive patients during the two study periods.
Spurling, 2007 Funding not reported	• Prospective cohort	• 13 out of the 14 (7 part-time general practitioners (GPs), 3 practice nurses, 3 regular reception staff, 1 practice manager) participated • Inala Health Centre General Practice in Brisbane, Australia	-Policy of reduced access to pharmaceutical sales representatives including: reception staff not to make appointments for representatives or accept promotional material; representatives	• Pre policy	• Number of prescription per patient (behavior) • Number of promotional materials (no further details provided) • Number of samples in the drug cupboard and time booked for pharmaceutical sales representatives	• Timeframe: 2004 • The policy was evaluated 3months pre policy and 9 months post policy • Data collected through audit and staff survey

			cannot access sample cupboards; GPs wishing to see representatives may do so outside consulting hours.		(actual implementation of the policy •	
Hartung, 2010 Funding in part by an American Academy of Family Physicians Foundation Research Stimulation Grant	• Segmented linear regression models using locally obtained pharmacy claims.	• The Madras Medical Group, a family practice clinic employing 5 physicians and 1 physician assistant;	• After the implementation of a policy restricting access of pharmaceutical sales representatives to the clinic was implemented	• Before the implementation of the a policy • Oregon Medicaid pharmacy claims were used to control for secular prescribing changes.	• Percentage of branded drug use (behavior) • Percentage of promoted drug use (behavior) • Average prescription costs (cost)	• Time Frame: April 1, 2004, to September 31, 2007. • In January 2006 the Medicare Part D program was implemented

Table 3: Risk of bias in included RCT

Study Name	Sequence generation	Allocation concealment	Blinding (participants, data collectors, outcome adjudicators)	Completeness of outcome data	Completeness of outcome reporting
Freemantle, 2000	Low risk "Practices were randomized to intervention or control using computer generated random numbers in a stratified scheme"	Unclear risk Not reported	Unclear risk Not reported	Low risk No missing data reported	Low risk No evidence of selective outcome reporting

Table 4: Risk of bias in included observational studies

Study Name	Developing and applying appropriate eligibility criteria	Measurement of exposure	Measurement of outcome	Controlling for confounding	Completeness of data
Boltri 2002	Low risk Physicians and residents in the control and exposed groups are of the same pool	Low risk Policy applied across the clinic	Low risk Data collection was based on medical records, and done by research assistant blinded to study design and hypothesis	Low risk "Logistic regression was then performed to adjust the odds ratio for the relation of physician type, prescribing patterns, and time."	Low risk No missing data reported
Spurling, 2007	Low risk Diaries chosen at random for a 1-month period .A random week was chosen to audit doctors' prescribing.	Low risk Policy applied across the clinic	Unclear risk Not clear whether the survey instrument was validated	High risk According to the authors, the possibility of confounding cannot be ruled out	Low risk. All except one returned the completed questionnaire
Hartung, 2010	Unclear risk	Low risk Policy applied across the clinic	Unclear risk Use of claim data; however validity of the data not described	Low risk They include "a contemporaneous control group of patients or clinicians also experiencing this potential confounder."	Low risk 'Although it is possible that some prescriptions would not have been captured by using data from only one pharmacy, it seems

				(confounding resulting from secular changes in prescribing).	unlikely that this subset would have introduced any systematic bias or loss of generalizability."

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None.

CONTRIBUTIONS OF AUTHORS

Concept and design: EAA, LA, KB

Study selection: LA, LK, HN, HB, RF

Data collection: LA, LK

Data analysis and interpretation: EAA, LA, LK, HB, KB

Drafting of the manuscript: EAA, LA

All authors reviewed and approved the submitted version of the manuscript.

DECLERATIONS OF INTEREST

None of the authors has conflicts of interest to declare.

DATA SHARING STATEMENT

No additional data available

Figure legend:

Figure 1: study flow

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Legislative, educational, policy, and other il~~i~~nterventions targeting physicians' interaction with pharmaceutical companies: A systematic review

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ABSTRACT

Background:

Pharmaceutical company representatives likely influence the prescribing habits and professional behavior of physicians.

Objective: The objective of this study was to systematically review the effects of interventions targeting practicing physicians' interactions with pharmaceutical companies.

Eligibility criteria: we included observational, non-randomized controlled trials, and randomized controlled trials evaluating legislative, educational, policy, or other interventions targeting the interactions between physicians and pharmaceutical companies

~~Methods~~**Data sources:**

~~We used the Cochrane approach to systematic reviews.~~ The search strategy included an electronic search of MEDLINE and EMBASE. Two reviewers completed in duplicate and independently study selection, data abstraction, and assessment of risk of bias.

Appraisal and synthesis methods: We assessed the risk of bias in each included study. We summarized the findings narratively because the nature of the data did not allow conducting a meta-analysis. We assessed the quality of evidence by outcome using the GRADE methodology.

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Results:

Of 119,189 identified citations, one randomized clinical trial and three observational studies met the eligibility criteria. All four studies specifically targeted one type of interaction with pharmaceutical companies, i.e., interactions with drug representatives. The RCT provided moderate quality evidence of no effect of a "collaborative approach" between the pharmaceutical industry and the health authority. The three observational studies provided low quality evidence suggesting a positive effect of policies aiming to reduce interaction between physicians and the pharmaceutical companies (in the form of restricting free samples, promotional material, and meeting with pharmaceutical company representatives) on prescription behavior.

Limitations: We identified a limited number of studies to allow strong conclusions.

Conclusion:

Available evidence suggests a potential impact of policies aiming to reduce interaction between physicians and drug representatives ~~the pharmaceutical companies~~ on physicians' prescription behavior. We identified no evidence about interventions affecting other types of interaction with pharmaceutical companies.

Article summary

Article focus

- To systematically review the effects of interventions targeting practicing physicians' interactions with pharmaceutical companies

Key messages

- There is a potential impact of policies aiming to reduce interaction between physicians and drug representatives on physicians' prescription behavior
- Potentially effective policies include: restricting free samples, promotional material, and meeting with pharmaceutical company representatives

Strengths and limitations of this study:

- We followed Cochrane methodology for conducting this systematic review.
- This is the first systematic review to focus on practicing physicians.
- We identified a limited number of studies to allow strong conclusions.

INTRODUCTION

Physicians may benefit from the relationship with pharmaceutical industry through access to information on new medications and products. However, the direct financial rewards provided to them could be used to persuade them to prescribe newer and more expensive drugs to patients.[1] One industry market study found that physician profiling could increase the uptake of new drugs by 30%.[2] On the other hand, studies conducted in different parts of the world (e.g., Canada, France the United States, Australia and Malaysia) have consistently found that risk and harmful effects of drugs were often missing in presentations by pharmaceutical representatives to doctors.[3]

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Examples of such interactions include contact with drug representatives, educational talks, and sponsored travel, etc.;

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We did not exclude studies based on date of publication, but excluded studies not published in English.

Search Strategy

We designed the search strategy with the help of a medical librarian (Appendix 1). The strategy included searching MEDLINE and EMBASE electronic databases using the OVID interface in ~~September~~ April 201~~4~~2. The search combined terms for physicians, and pharmaceutical, and included both free text words and medical subject heading. We did not use any search filter. The appendix provides the full details of the search strategies. Additional search strategies included search of the grey literature (theses and dissertations). Also, we reviewed the references lists of included and relevant papers.

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duplicate and independently the full texts for eligibility. They used a standardized and pilot tested screening form and resolved disagreement by discussion.

Data collection

Two reviewers independently abstracted in duplicate and independently data from eligible studies. They used a standardized and pilot tested screening form and detailed written instructions. They resolved disagreement by discussion. We calculated the agreement between the two authors for the assessment of trial eligibility using kappa statistic. The data abstracted included the type of study; the funding source; the characteristics of the population, exposure, and control; the outcomes assessed; and statistical data.

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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. According to recommendations outlined in the Cochrane Handbook, we used the following criteria for assessing the risk of bias in randomized studies:

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- Flawed measurement of both exposure and outcome (e.g., differences in measurement of exposure such as recall bias in case-control studies, differential surveillance for outcome in exposed and unexposed in cohort studies
- Failure to adequately control confounding (e.g., failure to accurately measure all known prognostic factors, failure to match for prognostic factors and/or adjustment in statistical analysis
- Incomplete follow-up

We graded each potential source of bias 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 in a narrative way. We assessed the quality of evidence by outcome using the GRADE methodology.[9]

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RESULTS

Results of the search ~~**Description of included studies**~~

Figure 1 shows the study flow. Of the 110,189 identified articles, three observational studies and one randomized trial met our inclusion criteria. We excluded 27 full-text articles for the following

reasons: studies assessed the association between interactions with pharmaceutical companies and behaviors (and effects of interventions) (n=15); and studies conducted among students or residents (n=12). The value of kappa statistic for full text screening was 0.893, reflecting high levels of agreement.

Description of included studies

Tables 1 and 2 show the characteristics of the included studies. All these studies assessed interventions that specifically targeted interactions of physicians with drug representatives. We identified no studies of interventions targeting other potential types of interaction with pharmaceutical companies (e.g., educational talks, sponsored travel).

These studies were conducted in Warwickshire in the United Kingdom, central Oregon in the United States, Brisbane in Australia, and Southeastern of the United States. Three studies evaluated the effects of the implementation of new legislations and regulatory policies [10 11] while one study evaluated the effects of various educational interventions[10]] These studies assessed the impact of intervention son physician knowledge, attitudes and behavior. The sample sizes in these studies also varied from 14 to 79.

Table 3 shows the assessment of the risk of bias in the one included RCT. The risk of bias was judged to be either low or unclear for the different criteria assessed [10].Table 4 shows the assessment of the risk of bias in the three included observational studies [7-9]. We judged the risk of bias associated with the exposure measurement and the completeness of data as low for all included studies. We judged the risk of bias as either low or unclear for the remaining methodological features, except for confounding which we judged as high risk for one study [12].

Effects of implementing new policies

As mentioned previously, one trial and three observational studies evaluated the effects of program or organizational policies that limit contact between physicians and pharmaceutical company representatives.

Freemantle et al,[13] conducted a randomized controlled trial to assess the "a collaborative approach" between the pharmaceutical industry and the local health authority. The collaborative approach consisted of post-graduate educational allowance accreditation and a letter from the pharmaceutical advisor asking the practice to agree to see the representative. ~~where b~~Both the intervention and the control groups received practice guidelines, routine marketing activity, and a routine H~~h~~ealth A~~a~~uthority advice. The authors do not provide further details about the "routine advice", but the Health Authorities in the United Kingdom apparently enact the directives of the Department of Health, implement its fiscal policy, and run or commission local health services.[14] ~~In addition, the interventional group received post-graduate educational allowance accreditation and a letter from the pharmaceutical advisorasking the practice to "agree to see the representative preceded approaches by company representatives to specific practices".~~The specific objective of the intervention was to substitute in primary care a proton inhibitor for an alternative deemed therapeutically equivalent but less costly, based on "evidence based guidelines". The investigators reported that p~~to assess the "additional benefits from a collaborative approach" between the pharmaceutical industry and the health authority. P~~rescribing in both groups "moved towards that

recommended by the guidelines". However, the proportion of prescriptions in line with the guidelines and the overall cost were not different between the two groups.

Boltri et al. [10]conducted a retrospective cohort study of a new policy prohibiting drug samples distribution (mainly hypertensive drugs). Participants included 24 family practice residents and 8 clinical attending physicians at an outpatient clinic in the southeastern United States. At six months after the new policy implementation, prescription of first-line medication increased from 38% to 61% (odds ratio (OR) =2.73, 95% CI=1.29, 5.76)

Spurling et al examined a cohort of 14 participants, 3 months prior and 9 months after the implementation of a new policy.[12] ~~that~~ This policy included: reception staff not making appointments for pharmaceutical sales representatives nor accepting promotional material; pharmaceutical sales representatives not accessing sample cupboards; and general practitioners wishing to see pharmaceutical sales representatives may do so outside consulting hours.

The investigators found that the number of overall promotional material were reduced by 32% and 21% at 3 and 9 months respectively post-intervention compared to pre-intervention. The number of samples was reduced by 59%, and 70% at 3 and 9 months respectively post-intervention compared to pre-intervention. The number of prescriptions per patient encounter fell from 0.99 pre-intervention to 0.92 and 0.54 at 3 and9 months post-intervention respectively. The number of generic prescriptions increased from 4% pre-intervention to 8.6% and 8.1% after 3 and 9 months post-intervention, respectively.

Hartung et al. [11]evaluated the effects of the implementation of new policies applied by the Madras Medical Group family practice clinics (Ohio, United States). The policies included discontinuing seeing pharmaceutical representatives and stopping acceptance and distributing drug samples. The control group consisted of a regionally discrete sample of the Oregon Medicaid program~~Medicaid enrollees who were not also enrolled in Medicare~~. Medicaid and Medicare are two governmental programs that provide medical and health-related services to specific groups of people in the United States. The analysis used segmented linear regression models to compare 92,223 and 178,028 pharmacy claims from the intervention and control groups covering 18 months before and 18 months after policy implementation. In aggregate, use of "promoted agents" decreased by 1.4% while the use of "non-promoted branded agents" increased by 3.0%. However, the results varied by the class of drug. Interestingly, the investigators found that the average prescription drug cost increased significantly (by USD 5.2) immediately after policy implementation.

Assessment of the quality of evidence

Following the GRADE methodology, we judged the quality of evidence from the RCT as moderate due to imprecision (only 79 participants). We judged the quality of evidence from observational studies as low due to study design. Indeed, overall risk of bias was judged as low, and we did not find any evidence of inconsistency, imprecision, indirectness or publication bias warranting further downgrading.

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Discussion

In summary, our systematic review identified one RCT[13] and three observational studies[10 11]. All included studies targeted one type of interaction with pharmaceutical companies, i.e., interactions with drug representatives. The RCT found no effect of a "collaborative approach" between the pharmaceutical industry and the health authority. The three observational studies found a positive effect on prescription behavior of clinic policies aiming to reduce interaction between physicians and the pharmaceutical companies (in the form of free samples, promotional material, and meeting with pharmaceutical company representatives). Our systematic review did not identify eligible studies assessing other relevant types of interactions between physicians and pharmaceutical companies, such as educational talks, sponsored travel.

A major strength of this study is the use of Cochrane methodology for conducting the systematic review. In addition, this is the first systematic review to focus on practicing physicians. Some of the limitations of this review relate to those of the included studies. Indeed, we identified a limited number of studies to allow strong conclusions. Also, the included studies suffered from risk of bias related to the lack of validity of outcome measurement, and the inadequate handling of significant potential confounders.

The available evidence does not provide clear answers on why a "collaborative approach" between the pharmaceutical industry and a health authority did not work, while policies restricting certain types of interaction between physicians and the pharmaceutical companies worked. It might be that

restriction approaches are easier to implement compared to more complex interventions such collaborative approaches. Also, it might be that the link between the restrictive interventions and the desired outcome is clearer and shorter compared with the collaborative interventions.

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~~The 2010 enactment of the Physician Payment Sunshine Act (PPSA) marks the first Congressional involvement in the regulation of disclosure related to pharmaceutical marketing.~~ , ~~(i,e. pharma companies will be recording payments to doctors--speaking fees, consulting arrangements, and free food)To prevent undue influence and protect the public fisc, a number of states began regulating these marketing practices, requiring companies to disclose all gifts to practitioners, prohibiting the commercialized sale of prescription data, and prohibiting certain gifts altogether.~~

~~The 2010 enactment of the Physician Payment Sunshine Act (PPSA) marks the first Congressional involvement in the regulation of disclosure related to pharmaceutical marketing.~~

~~Overall, the Act improves transparency in pharmaceutical marketing to physicians and expands the regulation of disclosure of pharmaceutical marketing activities in important substantive ways Between 1993 and 2011 a number of states and D.C. passed laws that (1) require manufacturers to disclose payments and gifts to physicians, (2) prohibit certain gifts altogether, (3) require the adoption of a compliance code, and (4) prohibit data mining of practitioners' prescribing patterns.[4] .~~

The Physician Payment Sunshine Act (PPSA) enacted in 2010 in the United States marks the first Congressional involvement in regulating the disclosure by physicians of payments by pharmaceutical companies. Under this Act, manufacturers of drugs, medical devices and biologicals participating in U.S. federal health care programs 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). The purpose is to prevent undue influence and protect the public interest.[4] The Sunshine Act could be viewed as a systems intervention targeting physicians' interactions with pharmaceutical companies. Although we have not identified at this point any study assessing the impact of this Act on the prescription behavior of physicians, we expect those studies to become available over the next few years.

While acknowledging the importance of regulation, some have called for physicians to take the lead and minimize any undue commercial influence on their profession.[5] Professional organization have a particularly important responsibility, given the relationships between physicians and the pharmaceutical industry may erode social trust in medical professionals.[5]

A 2005 joint report by the World Health Organization (WHO) and the Health Action International (HAI) reported on interventions to counter promotional activities.[15] The evidence presented in that report, although 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 their attitudes. At that time, the report called for research on interventions that could affect doctors' behavior.

We identified only one other systematic review of the literature addressing the same question but with residents and students instead of practicing physicians [8]. The review identified 12 eligible studies, seven before-after studies and three controlled trials. The findings suggested that well-

designed seminars, role-playing, and focused curricula could affect trainee attitudes and behavior. However, it was not clear whether these effects were sustainable long-term.

Implications for practice

Based on the evidence, health administrators aiming to reduce the negative impact of physicians' interaction with pharmaceutical companies may not want to spend their resources on "collaborative approaches" between pharmaceutical industry and the health authority. They ~~are more likely to~~may possibly benefit from implementing policies restricting free samples, industry supplied promotional materials, and meeting with pharmaceutical company representatives.

However, a potential limitation of implementing restriction policies is creating an "information gap" that has been filled so far by the pharmaceutical representatives (e.g., information on new drugs). Indeed, those representatives provide information to doctors about indications and dosages of medications to relatively high percentages of physicians [3]. Sales representatives are frequently the only source of information about medicines in developing countries where there may be as many as one representative for every five doctors[16].

As an alternative to complete restriction of interactions, some jurisdictions have attempted to regulate interactions. In Australia, the Australian Pharmaceutical Manufacturers Association has a code of conduct covering sales representatives. Although the code does not state what kind of information sales representatives must provide, it does insist that their presentations be current, accurate and balanced [16].

~~3. Sales representatives are frequently the only source of information about medicines in developing countries where there may be as many as one representative for every five doctors.~~

~~Most doctors think information from pharmaceutical companies is biased, but many think it is useful.~~

~~Sales representatives are frequently the only source of information about medicines in developing countries where there may be as many as one representative for every five doctors.~~

~~Sales representatives and other commercial sources were not evaluated highly, but sales representatives were the most frequent source of first information about medicines, and were one of the most frequently mentioned sources of information needed to prescribe.~~

~~In Australia, the Australian Pharmaceutical Manufacturers Association has a code of conduct covering sales representatives. Although the code does not state what kind of information sales representatives must provide, it does insist that their presentations be current, accurate and balanced [13].~~

Implications for research

Future studies should address the methodological limitations of the available evidence. This includes conducting well-designed randomized trials. Future observational studies should aim for proper assessment of the exposure, controlling for all confounders, and minimizing missing data. There is also a need for ~~Future~~ studies ~~should also consider~~of other types of interventions, ~~(including~~ e.g., educational ~~e.g., educational~~ and legislative interventions~~one~~), as well as target other types of interactions with pharmaceutical companies (e.g., educational talks, sponsored travel). As the Sunshine Act gets implemented, we expect over the next few years the publication of studies assessing its impact on the prescription behavior of physicians.

TABLES ~~AND FIGURES~~

Table 1: Characteristics of included RCT

Study Name	Study Design	Participants, setting	Exposure	Control	Outcomes	Notes
Freemantle, 2000 Funding by Warwickshire Health Authority	• Randomized controlled trial	• All 79 cardiovascular practices in Warwickshire participated in the trial.	• 40 practices who received, in addition to what the control group received: • Letter from the chief executive of the health authority • Postgraduate educational allowance accreditation • A letter from the pharmaceutical advisor	• 39 practices who received: • Practice guidelines • Routine marketing act • Routine health authority advice	• Proportion of prescriptions in line with the guidelines (behavior) • Prescribing costs	• Time frame: October 1997 and April 1998.

Table 2: Characteristics of included observational studies

Study Name and funding	Study Design	Participants, setting	Exposed group	Control group	Outcomes	Notes
Boltri 2002 Funding by the Health Resources and Services Administration	• Retrospective cohort • Charts from two time periods were reviewed for a diagnosis of hypertension	• 24 family practice residents and 8 clinical attending physicians faculty at the outpatient clinic of a family practice residency program in the southeastern United States.	• 507 hypertensive patients during "Period 2": January and February 1998 after the policy prohibiting samples distribution was implemented in august 1997	• 422 hypertensive patients during "Period 1": January and February1997before the policy prohibiting samples distribution was implemented.	• Effect of policy on prescription of first line hypertension drugs versus prescription of second-line drugs by all physicians (by JNC VI)	• Data collection of the outcome was based on the medical reports of all hypertensive patients during the two study periods.
Spurling, 2007 Funding not reported	• Prospective cohort	• 13 out of the 14 (7 part-time general practitioners (GPs), 3 practice nurses, 3 regular reception staff, 1 practice manager) participated • Inala Health Centre General Practice in Brisbane, Australia	-Policy of reduced access to pharmaceutical sales representatives including: reception staff not to make appointments for representatives or accept promotional material; representatives	• Pre policy	• Number of prescription per patient (behavior) • Number of promotional materials (no further details provided) • Number of samples in the drug cupboard and time booked for pharmaceutical sales representatives	• Timeframe: 2004 • The policy was evaluated 3months pre policy and 9 months post policy • Data collected through audit and staff survey

			cannot access sample cupboards; GPs wishing to see representatives may do so outside consulting hours.		(actual implementation of the policy •	
Hartung, 2010 Funding in part by an American Academy of Family Physicians Foundation Research Stimulation Grant	• Segmented linear regression models using locally obtained pharmacy claims.	• The Madras Medical Group, a family practice clinic employing 5 physicians and 1 physician assistant;	• After the implementation of a policy restricting access of pharmaceutical sales representatives to the clinic was implemented	• Before the implementation of the a policy • Oregon Medicaid pharmacy claims were used to control for secular prescribing changes.	• Percentage of branded drug use (behavior) • Percentage of promoted drug use (behavior) • Average prescription costs (cost)	• Time Frame: April 1, 2004, to September 31, 2007. • In January 2006 the Medicare Part D program was implemented

Table 3: Risk of bias in included RCT

Study Name	Sequence generation	Allocation concealment	Blinding (participants, data collectors, outcome adjudicators)	Completeness of outcome data	Completeness of outcome reporting
Freemantle, 2000	Low risk "Practices were randomized to intervention or control using computer generated random numbers in a stratified scheme"	Unclear risk Not reported	Unclear risk Not reported	Low risk No missing data reported	Low risk No evidence of selective outcome reporting

Table 4: Risk of bias in included observational studies

Study Name	Developing and applying appropriate eligibility criteria	Measurement of exposure	Measurement of outcome	Controlling for confounding	Completeness of data
Boltri 2002	Low risk Physicians and residents in the control and exposed groups are of the same pool	Low risk Policy applied across the clinic	Low risk Data collection was based on medical records, and done by research assistant blinded to study design and hypothesis	Low risk "Logistic regression was then performed to adjust the odds ratio for the relation of physician type, prescribing patterns, and time."	Low risk No missing data reported
Spurling, 2007	Low risk Diaries chosen at random for a 1-month period .A random week was chosen to audit doctors' prescribing.	Low risk Policy applied across the clinic	Unclear risk Not clear whether the survey instrument was validated	High risk According to the authors, the possibility of confounding cannot be ruled out	Low risk. All except one returned the completed questionnaire
Hartung, 2010	Unclear risk	Low risk Policy applied across the clinic	Unclear risk Use of claim data; however validity of the data not described	Low risk They include "a contemporaneous control group of patients or clinicians also experiencing this potential confounder."	Low risk 'Although it is possible that some prescriptions would not have been captured by using data from only one pharmacy, it seems

				(confounding resulting from secular changes in prescribing).	unlikely that this subset would have introduced any systematic bias or loss of generalizability."

~~Figure 1: Study flow~~

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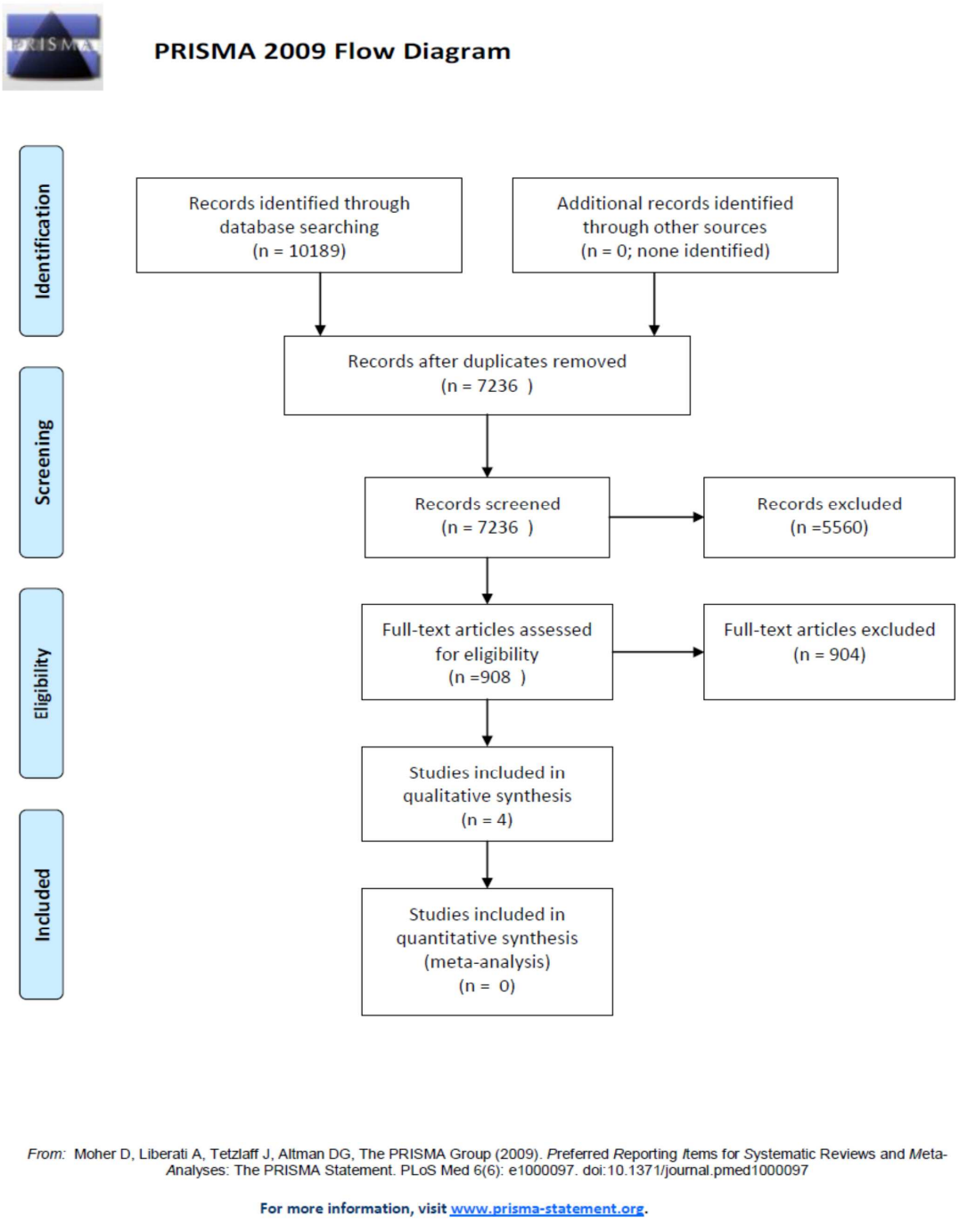

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Contributions of authors

Concept and design: EAA, LA, KB

Study selection: LA, LK, HN, HB, RF

Data collection: LA, LK

Data analysis and interpretation: EAA, LA, LK, HB, KB

Drafting of the manuscript: EAA, LA

All authors reviewed and approved the submitted version of the manuscript.

DECLERATIONS OF INTEREST

None of the authors has conflicts of interest to declare.

FUNDING

None.

Figure legend:

Figure 1: study flow

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APPENDICIES

Appendix 1: Search strategy

Medline 1946 to October Week 2 2012

1. Conflict of Interest.mp.or "Conflict of Interest"/
2. Drug Industry/
3. Gift Giving/
4. detailman.mp.
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8. doctor*.mp.
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10. primary care.mp.
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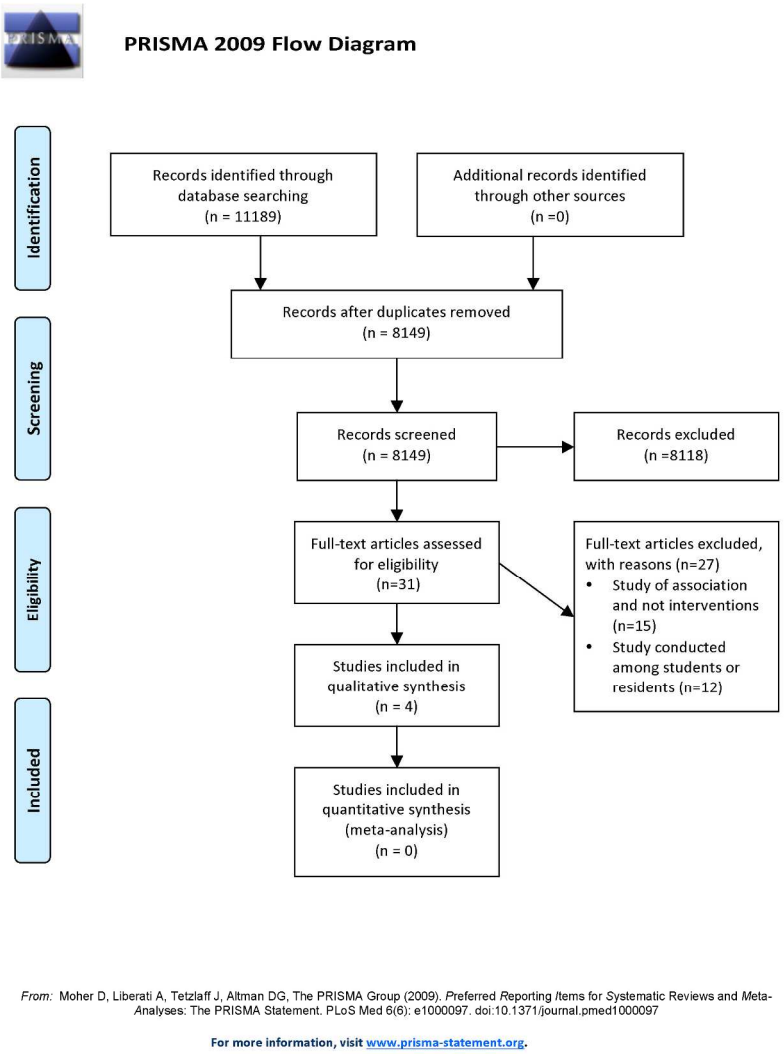

Study flow
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APPENDICIES

Appendix 1: Search strategy

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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, 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	No
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.	4, 5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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).	5, 6
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6, 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
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.	7

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).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
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.	7, 8
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.	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).	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.	9, 10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
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).	11
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).	11, 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13, 14
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.	22

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

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