PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Legislative, educational, policy, and other interventions targeting physicians' interaction with pharmaceutical companies: A systematic review
AUTHORS	Alkhaled, Lina; Kahale, Lara; Nas, Hala; Brax, Hneine; Fadlallah, Racha; Badr, Kamal; Akl, Elie

VERSION 1 - REVIEW

REVIEWER	Murat Civaner Uludag University School of Medicine, Bursa, Turkey
REVIEW RETURNED	01-Mar-2014

GENERAL COMMENTS	I would like to congratulate my colleagues for choosing this subject and carrying out a systematic review, which requires a hard-work and is really needed in order to assess the effectiveness of the initiatives aiming to cope with negative impact of marketing methods. I just would like to suggest some minor points to improve the paper: - Including the studies done with medical students and residents would be valuable, as it a) increases the number of studies in the review, b) could give an insight on the effectiveness of educational initiatives. - I think the Discussion section should be expanded, especially the subsection "Implications for practice". For instance: It is widely claimed that limiting the exposure to the marketing methods (incl. meeting with representatives) would be the most efficient intervention, which I personally support. But this claim should always be supported with a concrete suggestion about how to fill the gap (of information on new drugs, research funds, samples etc). Also, more information on "collaborative approaches" would give more clearer picture on what to do. - I recommend a WHO/HAI publication to consider: "Drug Promotion - What We Know, What We Have Yet to Learn - Reviews of Materials in the WHO/HAI Database on Drug Promotion" by Norris P, et al. (http://apps.who.int/medicinedocs/en/d/Js8109e/) This is an invaluable resource, which has a specific section on the effective and ineffective interventions to cope with marketing methods (titled "What interventions have been tried to counter promotional activities, and with what results?"). I believe it will be

	very helpful for Discussion.

REVIEWER	Gisela Schott Drug Commission of the German Medical Association
REVIEW RETURNED	07-Mar-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER	Susan L. Norris Associate Professor Oregon Health and Science University I have performed research on conflict of interest and guideline development, and am a member of the GRADE Working Group. I have no financial interests to declare.
REVIEW RETURNED	10-Mar-2014

GENERAL COMMENTS	Major comments 1. The intervention that is the focus of the systematic review was not clear until the results section. The title refers to interactions with pharma companies, however the objectives and results focus only on interactions with drug reps. Drug reps are one way for docs to interact with pharma, but there are others, for example giving educational talks or accepting sponsored travel. In addition, in Table 1, Freemantle, the intervention includes “postgraduate educational allowances” . How does that relate to interactions with drug reps? 2. The study search ended in September 2012, which is too old. It needs to be updated. 3. The implications for practice section is weak and I think the statement that “they are more likely to benefit from … policies restricting …. samples, etc” is an overstatement, given the uncertainty of the effect (low quality evidence). 4. The discussion section is very weak. Why might some interventions work and others not? Could you tie your findings in to the Sunshine Act? More detail on future research would be interesting. 5. The manuscript requires extensive technical editing by a native English writer prior to acceptance. The language is repetitive, the text can be tightened up considerably, and there are many grammatical errors. The following are a few examples of unclear text, but there are numerous others. a. Abstract page 2: “suggesting a positive effects of policies aiming to reduce interaction (in the form of free samples, promotional material…”. This is unclear, as “reduce interaction” could refer to giving free samples, etc, rather than reducing free samples. b. Repeatedly throughout the manuscript he phrase “two reviewers completed in duplicate independently …” This is redundant. Why not something like “two independent reviewers…” or “two reviewers independently examined…”? c. Kappa is mentioned twice: page 6 and 7. This is unnecessary. d. Page 8 “routine marketing act, and a routine health authority advice”. What does this mean? e. Page 10: The sentence beginning “The control group consistent of a regionally discrete sample of Medicaid enrollees..” is unclear to non-US readers, and why would this group serve as the control? 6. The search strategies on page 20 are not complete. I assume all terms were combined by “or”, but this is not explicit. In addition, the

	language restriction should be apparent in the search. Minor comments 1. Page 4: inclusion criteria: what does “cohort” study mean? The included studies all had a comparator, so the study design criteria could be more clear. 2. The paragraph on GRACE assessment in the discussion should be moved to the results section.

VERSION 1 – AUTHOR RESPONSE

1- Reviewer Name: Murat Civaner
Institution and Country: Uludag University School of Medicine,
Bursa, Turkey

Please state any competing interests or state ŒNone declared¹: I have nocompeting interest to declare.

“Just a couple of comments: the search could be updated and the title could be more specific. The context of the study with respect to other research in the area seems a bit thin.”

Thank you for the suggestions. We have updated the search on April 1st 2014. We have identified no newly eligible study published since the date we ran our former search. We have updated the study flow diagram accordingly.

We have also edited the title to make it more specific as follows:
“Legislative, educational, policy, and other interventions targeting physicians’ interaction with pharmaceutical companies: A systematic review”

Regarding the context, we now provide more details in the background section:
“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]”

“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]”

“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]”

2- Reviewer Name: Gisela Schott
Institution and Country: Drug Commission of the German Medical Association

Please state any competing interests or state: None declared

“I would like to congratulate my colleagues for choosing this subject and carrying out a systematic review, which requires a hard-work and is really needed in order to assess the effectiveness of the initiatives aiming to cope with negative impact of marketing methods.

Thank you for the highly positive feedback and for the very constructive suggestions.

I just would like to suggest some minor points to improve the paper:

- Including the studies done with medical students and residents would be valuable, as it a) increases the number of studies in the review, b)could give an insight on the effectiveness of educational initiatives.

Thank you for the suggestion. Our a priori objective was to assess interventions among practicing physicians. As a result we designed our search strategy to capture relevant papers relating to physicians and not to other groups. Thus, our search might have identified some, but not all studies assessing interventions among students. Inclusion of the identified ones would not provide a comprehensive and accurate interpretation of the available evidence.

At the same time, we do agree that data from studies of medical students might provide valuable information. As a result, we do refer and discuss the findings of an already published systematic review addressing medical students:

“We identified only one other systematic review of the literature addressing the same question but with residents and students 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.”

- I think the Discussion section should be expanded, especially the subsection ³Implications for practice². For instance: It is widely claimed that limiting the exposure to the marketing methods (incl meeting with representatives) would be the most efficient intervention, which I personally support. But this claim should always be supported with a concrete suggestion about how to fill the gap (of information on new drugs, research funds, samples etc).

Thank you for the suggestion. We have expanded the implications for practice section as follows:
“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 doctors13.

As an alternative to complete restriction of interactions, some jurisdictions have attempted to regulate them. 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.”

Also, more information on ³collaborative approaches² would give clearer picture on what to do.

We agree with the reviewer that this was not described in enough details. We have now expanded that paragraph as follows:
“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."

- I recommend a WHO/HAI publication to consider:
[3]Drug Promotion - What We Know, What We Have Yet to Learn - Reviews ofMaterials in the WHO/HAI Database on Drug Promotion[2] by Norris P, et al.
(http://apps.who.int/medicinedocs/en/d/Js8109e/)
This is an invaluable resource, which has a specific section on the effective and ineffective interventions to cope with marketing methods (titled [3]What interventions have been tried to counter promotional activities, and with what results?[2]). I believe it will be very helpful for Discussion."

Thank you pointing us to this important report. We have added a whole paragraph in the discussion section to highlight its findings:
"A 2005 joint report by the World Health Organization (WHO) and the Health Action International (HAI) reported on interventions to counter promotional activities.[16] 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."

3- Reviewer Name: Susan L. Norris
Institution and Country: Associate Professor at Oregon Health and Science University,Portland, OR 97229 USA

Please state any competing interests or state None declared[1]: I have performed research on conflict of interest and guideline development, and am a member of the GRADE Working Group. I have no financial interests to declare.

"Major comments

1. The intervention that is the focus of the systematic review was not clear until the results section. The title refers to interactions with pharma companies, however the objectives and results focus only on interactions with drug reps. Drug reps are one way for docs to interact with pharma, but there are others, for example giving educational talks or accepting sponsored travel. In addition, in Table 1, Freemantle, the intervention includes [3]postgraduate educational allowances[2] . How does that relate to interactions with drug reps?

Thank you for asking this important question. It has helped us make our objective clearer and less ambiguous.

Indeed, our objective was to systematically review the effects of interventions targeting physicians' interactions with pharmaceutical companies in general. However, we have not identified any eligible studies targeting types of interaction with pharmaceutical companies other than interaction with drug representatives.

We have tried to clarify to this point by making the following clarifications or additions in the manuscript:

• Abstract, Results section: "All four studies specifically targeted one type of interaction with pharmaceutical companies, i.e., interactions with drug representatives."
• Abstract, Conclusion section: "We identified no evidence about interventions affecting other types of interaction with pharmaceutical companies."
• Main text, Eligibility Criteria section: "Types of interventions: legislative, educational, policy, or other interventions targeting the interaction between physicians and pharmaceutical companies. Examples of such interactions include these include interactions with drug representatives, educational talks, sponsored travel, etc."
• Main text, Description of included studies section: "Tables 1 and 2 show the characteristics of the included studies. All these studies specifically targeted interactions of physicians with drug representatives. We identified no study targeting other potential types of interaction with pharmaceutical companies (e.g., educational talks, sponsored travel)."
• Main text, Discussion section: "In summary, our systematic review identified one RCT [9] and three observational studies, [6 -8] all specifically targeting one type of interaction with pharmaceutical companies, i.e., interactions with drug representatives."
• Main text, Discussion section: "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."
• Main text, Implications for research section: "Future studies should also consider 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)."

2. The study search ended in September 2012, which is too old. It needs to be updated.

Thank you for the suggestion. We have updated the search on April 1st 2014. We have identified no newly eligible study published since the date we ran our former search. We have updated the study flow diagram accordingly.

3. The implications for practice section is weak and I think the statement that ³they are more likely to benefit from policies restricting samples; etc² is an overstatement, given the uncertainty of the effect (low quality evidence).

Thank you for the remark. We agree with your judgment and have reworded the statement to tone it down as follows:
"They may possibly benefit from implementing policies restricting…"

We have also expanded the implications for practice section as follows:
"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 physicians3 .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 doctors13.

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 13."

4. The discussion section is very weak. Why might some interventions work and others not? Could you tie your findings in to the Sunshine Act? More detail on future research would be interesting.

Thank you for the suggestions. We have added the following text to try to explain the findings:
"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."

We have added the following text about the Sunshine Act to the discussion section:
"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."

We have added the following text to the implications for practice section:
"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 physicians3 .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 doctors13.

As an alternative to complete restriction of interactions, some jurisdictions have attempted to regulate them. 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."

We have added the following text to the implication for research section:
"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 get implemented, we expect the publication of studies assessing its impact on the prescription behavior of physicians."

5. The manuscript requires extensive technical editing by a native English writer prior to acceptance. The language is repetitive, the text can be tightened up considerably, and there are many grammatical errors. The following are a few examples of unclear text, but there are numerous others.

Thank you for all suggestions. We have adopted them as carefully reviewed the entirety of the text and made any necessary corrections and clarifications. Please see below.

(i) Abstract page 2: ³suggesting a positive effects of policies aiming to reduce interaction (in the form of free samples, promotional materials².
This is unclear, as ³reduce interaction² could refer to giving free samples, etc, rather than reducing free samples.

Thank you for the suggestion. We have now clarified it as follows: "in the form of restricting free samples, promotional material, and meeting with pharmaceutical company representatives"

(ii) Repeatedly throughout the manuscript he phrase ³two reviewers completed in duplicate independently Š² This is redundant. Why not something like ³two independent reviewersŠ² or ³two reviewers independently examinedŠ²?

Thank you for the suggestion. We have now adopted the following wording suggestion: "Two reviewers independently screened"

(iii) Kappa is mentioned twice: page 6 and 7. This is unnecessary.

Thank you for noting this. We now mention it only once.

(iv) Page 8 ³routine marketing act, and a routine health authority advice².
What does this mean?

Thank you for raising this question. We had mistakenly wrote "act" instead of "activity". We have now made the correction so it reads "routine marketing activity".

Unfortunately, the paper does not detail what "routine health authority advice" exactly refers to. Searching the Internet, there is some information suggesting that Health Authorities are part of the structure of the National Health Service (NHS). Apparently, they are responsible for enacting the directives and implementing fiscal policy as dictated by the Department of Health at a regional level, and have the responsibility for running or commissioning local NHS services. For now, we have made the following clarification:
"The authors do not provide further details, but the Health Authorities in the United Kingdom apparently enact the directives and implement fiscal policy as dictated by the Department of Health. They also run or commission local NHS services."

(v) Page 10: The sentence beginning ³The control group consistent of a regionally discrete sample of Medicaid enrollees..² is unclear to non-US readers, and why would this group serve as the control?

We have added the following clarification:
“Medicaid and Medicare are two governmental programs that provide medical and health-related services to specific groups of people in the United States.”

Unfortunately, the authors do not explicitly justify the selection of their control group, but most likely the choice was based on the fact that this group would be similar to the intervention group (same state) except for the intervention that was only applied to the intervention group. We have now further clarified this relationship as follows:
“Hartung et al. 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.”

6. The search strategies on page 20 are not complete. I assume all terms were combined by ³or², but this is not explicit. In addition, the language restriction should be apparent in the search.

Thank you for noting this important omission. We have added the four lines that were missing for both the MEDLINE and EMBASE strategies (Please refer to Appendix 1).

Minor comments:
1) Page 4: inclusion criteria: what does ³cohort² study mean? The included studies all had a comparator, so the study design criteria could be more clear.

Thank you for raising the question. We have clarified it as follows:
“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”

2) The paragraph on GRACE assessment in the discussion should be moved to the results section.”

Thank you for the suggestion. We have moved this section to the results section and included a reference to the GRADE methodology in the methods section.

VERSION 2 – REVIEW

REVIEWER	Susan L. Norris Oregon Health and Science University Portland, OR, USA
REVIEW RETURNED	04-Jun-2014

GENERAL COMMENTS	This manuscript has much improved, and my prior concerns have been addressed. It still needs some additional editing by a native English-speaking technical writer.