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Evidence of conflicts of interest in Medicine

Evidencia sobre conflictos de intereses en medicina

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Abstract

Introduction: Physicians' main responsibility is to practice medicine for the benefit of patients. However, there are situations where secondary interests affect this commitment and give rise to conflicts of interest.

Objective: To analyze currently available systematic reviews and meta-analyses on conflicts of interest in medicine to summarize relevant evidence in this regard.

Material and methods: A literature search was performed in the MEDLINE and LILACS databases using the following search strategy: systematic reviews and meta-analysis on conflicts of interests in medicine published in serialized scientific journals; no publication time or language limits were applied. Studies that met the inclusion criteria were grouped according to the medical activity they assessed, and information on the type and number of studies and conclusions of all publications included in the review was collected.

Results: 29 publications were included, and they were classified as follows: studies based on research articles, on clinical practice guidelines, on clinical practice, and on patient-oriented papers.

Conclusions: It was found that the authors of the original research papers included in the meta-analyses and systematic reviews analyzed here do not always state if they have conflicts of interest or not. Nevertheless, when said conflicts are reported, they tend to present results favoring the drugs or medical technologies of their sponsor.

Keywords: Conflict of Interest; Review; Medicine (MeSH).

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Resumen

Introducción. La principal responsabilidad de los médicos es la de actuar en beneficio de los pacientes; sin embargo, existen situaciones en las cuales surgen intereses secundarios que pueden afectar este compromiso y generar conflictos de intereses.

Objetivo. Analizar las revisiones sistemáticas y los metaanálisis actualmente disponibles en la literatura sobre el conflicto de intereses en medicina para sintetizar la información al respecto.

Materiales y métodos. Se realizó una búsqueda en las bases de datos MEDLINE y LILACS mediante la siguiente estrategia de búsqueda: revisiones sistemáticas y metaanálisis sobre conflictos de intereses en medicina publicados en revistas científicas seriadas; no se aplicaron restricciones de idioma o año de publicación. Los estudios que cumplieron con los criterios de inclusión fueron agrupados según la actividad médica evaluada; además, de cada uno de ellos se extrajo la cantidad y el tipo de estudios y las conclusiones.

Resultados. Se seleccionaron 29 publicaciones que se agruparon en estudios basados en artículos de investigación, en guías de práctica clínica, en la práctica clínica, y en publicaciones orientadas a los pacientes.

Conclusiones. Los estudios originales incluidos en las revisiones sistemáticas y los metaanálisis analizados en el presente estudio no siempre reportan los conflictos de intereses; sin embargo, cuando estos se mencionan, hay una tendencia a presentar resultados que favorecen el medicamento o la tecnología del patrocinador.

Palabras clave: Conflicto de intereses; Revisión; Medicina (DeCS).

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Introduction

Patient care, medical research, and continuing health education should be transparent processes, but this is not usually the case. It is common for physicians to receive gifts from a pharmaceutical laboratory and then prescribe the product of the company that acts as a benefactor. In this regard, some authors have reported that simple gifts, such as a meal, have led physicians to change the prescription of medicines to a particular brand.¹⁻³ In the case of research, scientists may be inclined to avoid publishing results that are unfavorable to the product that is funding the study.⁴

It is also common for medical societies to finance congresses with contributions from the pharmaceutical and medical technology industry. This financial support is invested not only in logistics, but in travel allowances, accommodation, and food for both speakers and attendees; this support may even go as far as sponsoring conferences as a clearly established marketing plan. This situation may also influence the presentation of outcomes that favor the sponsors.

These examples give an account of how doctors are being used as marketing agents.⁵ This may constitute a conflict of interest that can be understood as a situation where a judgment or action, which should be determined by a primary value established for professional or ethical reasons (protection of research subjects, obtaining safe knowledge and adequate care for the patient in the case of health), may be influenced or appear biased to obtain a secondary benefit.⁶

In Colombia, Article 106 of Act 1438 of 2011⁷ —amended through Article 133 of Act 1474 of 2011⁸ and Article 17 of Act 1751 of 2015—⁹ prohibits pharmaceutical companies that produce drugs and medical supplies from granting perks or gifts to professionals working in the health sector. Also, in 2018, the Ministry of Health and Social Promotion issued Resolution 2881, which requires pharmaceutical companies to report payments to any actor involved in the system.¹⁰

Systematic reviews are a type of scientific investigation that uses primary original studies as their unit of analysis to answer a formulated research question utilizing a systematic and explicit process of analysis of said original studies. Meta-analyses, on the other hand, are reviews that use statistical methods to combine the results of two or more studies.¹¹⁻¹³

With this in mind, an analysis of the systematic reviews and meta-analyses on conflicts of interest in medicine currently available was performed to synthesize information in this regard.

Materials and methods

A search for studies on conflicts of interest in medicine published in serialized scientific journals available in MEDLINE and LILACS was done. In MEDLINE, the search was conducted on February 10, 2018, using the MeSH term “conflict of interest” and the filters “Meta-Analysis” and “Systematic Review.” In turn, the search in LILACS was conducted on February 18, 2018, using the DeCS term “Conflicto de interés” (Spanish for conflict of interest) and the filter “Systematic Review.” There were no language or publication date restrictions.

First, to determine whether the studies met the inclusion criteria (being a systematic review or a meta-analysis assessing conflicts of interest in some medical area), two reviewers independently scanned the title and abstract of the publications found in the initial search. The full texts of the selected publications were then analyzed by the author of this study to obtain the final sample for the review.

The publications selected during the search for analyses were grouped according to the main activity evaluated: research articles (reviews not involving direct clinical interaction), clinical practice guidelines (CPG), reviews based on clinical practice (evaluation of medical or surgical treatments), and patient-oriented publications.

Results

The search yielded 2 025 references in MEDLINE and 11 in LILACS, of which 29 were selected due to their relevance and design; all were taken from the MEDLINE database (Figure 1). The selected publications were grouped according to the activity evaluated (Tables 1, 2, 3 and 4).

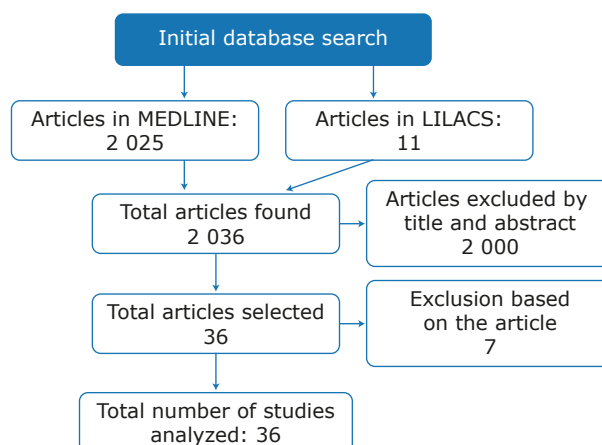


Figure 1. Selection process of articles for analysis. Source: Own elaboration.

Research articles

Nine reviews were based on research articles (Table 1), of which 4 clearly presented the association between sponsorship and outcomes; 3 did not assess the impact of having a conflict of interest; 1, which included Latin American and Caribbean publications, warns that funding for experimental studies is often ambiguous or unreported; and 1, which is a meta-analysis that analyzes preclinical trials in animals, did not find any difference between disclosing or not the financial conflict of interest.¹⁴⁻²²

Clinical practice guidelines

According to the search criteria, there were 9 CPG reviews (Table 2), of which 7 concluded that there is low disclosure rates of conflicts of interest.²³⁻²⁹ However, Feuerstein, in different studies and with the support of several researchers, highlights that this type of publication has multiple conflicts of interest.²³⁻²⁷ The other 2 reviews do not address this issue.³⁰⁻³¹

Table 1. Systematic reviews and meta-analyses on conflict of interest in research articles.

Author Year	Assessment	Number of studies	Type of study	Conclusions
Krauth <i>et al.</i> ¹⁴ 2014	Preclinical trials in animal (meta-analysis)	63	Experimental design studies.	The efficacy of statins was not altered by the disclosure of the financial conflicts of interest. Further studies are necessary to establish the possible causes of the differences between industry-sponsored and non-industry-sponsored studies, such as selective outcome reporting.
Bekelman <i>et al.</i> ¹⁵ 2003	Scope, impact, and management of financial conflicts of interest in biomedical research (meta-analysis)	37	16 cross-sectional surveys, 3 secondary data analyses, 15 systematic reviews and 3 content analyses	Financial relationships between industry, scientific researchers and academic institutions are widespread. Conflicts of interest arising from these ties can influence biomedical research in important ways.
Amiri <i>et al.</i> ¹⁶ 2014	Conflicts of interest and levels of evidence in spinal research results	864	49 level 1 studies, 200 level 2 studies, 106 level 3 studies, and 509 level 4 studies	A significant association is shown between funding source, study outcome and low levels of evidence in spinal research. A large proportion of industry-funded research was shown to provide level 4 evidence and report favorable outcomes.
Lundh <i>et al.</i> ¹⁷ 2017	More favorable outcomes and different risk of bias in industry-sponsored drug and device studies compared to studies that have other sources of funding.	75	58 clinical trials, 2 observational studies and 15 clinical and observational trials	Sponsorship of drug and device studies by the manufacturing company leads to more favorable efficacy results and conclusions than sponsorship by other sources. Analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments.
Revez <i>et al.</i> ¹⁸ 2013	Randomized clinical trials published in Latin America and the Caribbean according to funding source.	526	Randomized clinical trials	Some differences between publicly and non-publicly funded randomized clinical trials were found in clinical research for trial registration, ethic issues, conflict of interest reporting and trial settings among others.
Bes-Rastrollo <i>et al.</i> ¹⁹ 2013	Conflicts of interest in systematic reviews on sugar-sweetened beverages.	18	Systematic reviews	Systematic reviews with financial conflicts of interest were five times more likely to present a conclusion of no positive association between sugar-sweetened beverages consumption and obesity.
Alkhaled <i>et al.</i> ²⁰ 2014	Effects of interventions that assess the relationship between physicians and pharmaceutical companies	4	1 randomized trial, 2 cohorts and 1 linear regression model	Available evidence suggests a potential impact of policies aiming to reduce interaction between physicians and drug representatives on physicians' prescription behavior. There was no evidence concerning interventions affecting other types of interaction with pharmaceutical companies.
Hui <i>et al.</i> ²¹ 2012	Conflict of Interest in supportive and palliative oncology literature	848	429 case series, 72 cohort studies, 149 cross-sectional studies, 56 qualitative studies, 47 randomized trials and 95 studies with other designs.	A majority of supportive/palliative oncology studies did not report funding sources and conflict of interest, raising the need for standardization.
Schoenthaler <i>et al.</i> ²² 2014	Clinical trials on urolithiasis	110	16 level 1 studies, 15 level 2 studies, 23 level 3 studies and 56 level 4 studies.	90% of the publications declared conflicts of interest, whereas sponsoring of studies was declared only by one-third. A considerable number of trials involved issues of high commercial impact.

Source: Own elaboration.

Table 2. Systematic reviews of conflict of interest in clinical practice guidelines.

Authors Year	Assessment	Number of studies	Type of studies	Conclusions
Feuerstein <i>et al.</i> ²³ 2016	Overall quality of recommendations and conflict of interest in CPGs for Barrett's esophagus	8	CPG on Barrett's esophagus.	Half of the guidelines disclosed whether there was a conflict of interest; 75% of them reported potentially relevant conflicts of interest. There was evidence of the need to improve the process of CPG development, which are fundamental to maintaining a reliable health system.
Feuerstein <i>et al.</i> ²⁴ 2013	Quality of scientific evidence and conflicts of interest in gastroenterology CPGs.	81	CPG	Most guidelines failed to disclose the conflicts of interest, but when they became known, they were numerous.
Feuerstein <i>et al.</i> ²⁵ 2016	Determination of the validity of hip and knee osteoarthritis guidelines	13	CPG	Half of CPGs' recommendations for hip and knee osteoarthritis are based on poor-quality evidence. Almost as many fail to reveal relevant conflicts of interest, but they are evident when they are disclosed.
Feuerstein <i>et al.</i> ²⁶ 2013	CPG	19	CPG	Most guidelines do not disclose any conflicts of interest, but they are numerous when commented upon. In addition, they are not often updated and there is a lack of consensus among medical societies among the guidelines reviewed.
Feuerstein <i>et al.</i> ²⁷ 2014	Validity of the CPGs published by the interventional medical societies	149	CPG	Most of the intervention CPGs did not disclose conflicts of interest or level of evidence, but when they did, it was of low quality.
Norris <i>et al.</i> ²⁸ 2011	Conflict of interest in CPGs development	12	CPG	There is little information on the high prevalence of conflict of interest among CPG authors, and there are only case studies on their effect on guideline recommendations. Further research is needed to explore this potential source of bias.
Khalil <i>et al.</i> ²⁹ 2012	CPG	126	CPG	There is a substantial variation in the percentage of authors with potential conflicts of interest among guideline writing groups in the different medical societies selected by convenience sampling. However, several of these CPGs do not include potential conflicts of interest in their published guidelines.
Raftery <i>et al.</i> ³⁰ 2008	CPGs in the United Kingdom	3	Cross-sectional surveys: 2 RCTs and 1 mixed study (ACE-cohort study)	There was a low level of evidence about whether payments to health professionals increase their involvement in testing or patient recruitment.
Tibau <i>et al.</i> ³¹ 2015	CPG	142	91 CPGs and 51 consensus meetings.	Support for a specific drug is more common when the authors have financial conflicts of interest with the company marketing that drug. However, there is not enough evidence supporting an association between the funding of CPGs or consensus by the industry and said support.

RCT: randomized controlled trials; CPG: clinical practice guidelines.

Source: Own elaboration.

Reviews based on clinical practice

The search yielded 8 reviews based on clinical practice (Table 3), of which 7 highlight the tendency to present results that favor the drug or commercial sponsor.

The other review shows that conventional treatment is favored over the experimental metal-on-metal hip prosthesis arm.

Table 3. Systematic reviews on conflict of interest in reviews based on clinical practice.

Authors Year	Assessment	Number of studies	Type of studies	Conclusions
Fickweiler <i>et al.</i> ³² 2017	Prescription	49	43 cross-sectional studies, 2 cohort studies, 3 RCTs and 1 case-control study.	The interaction between physicians, the pharmaceutical industry, and its sales representatives, as well as the acceptance of gifts from the company's sales representatives, have been found to affect physicians' prescribing behavior and are likely to contribute to irrational prescribing of the company's drug.
DeGeorge <i>et al.</i> ³³ 2015	Surgical technique	124	69 retrospective studies, 1 high-quality study, 12 low-quality studies and 42 poor-quality or unclassified studies.	Studies disclosing an industry conflict are significantly associated with reporting lower postoperative complications
Hsu <i>et al.</i> ³⁴ 2012	Surgical technique	64	No level 1 studies, 10 level 2 studies, 7 level 3 studies, and 47 level 4 studies	Authors with financial conflicts have contributed to the increase in negative outcomes reported in the literature regarding the experimental treatment of metal-on-metal total hip arthroplasty; that is, the standard treatment is better than the experimental treatment.
Sung <i>et al.</i> ³⁵ 2013	Drug	66	56 RCTs, 9 cohort studies and 1 pseudo-experimental study.	About half of studies on the effect of botulinum toxin A in cerebral palsy were sponsored by the industry. Qualitative conclusions in those studies are more favorable to the use of the botulinum toxin A than the non-industry-sponsored studies. Therefore, clinicians should be aware of an industry-related conflict of interest regarding reports on the efficacy of botulinum toxin A injections in patients with cerebral palsy.
Riaz <i>et al.</i> ³⁶ 2016	Cardiovascular clinical trials (phase 2 and 3)	114	RCT	Authors' conflicts are associated with favorable outcomes in cardiovascular outcome trials.
Printz <i>et al.</i> ³⁷ 2013	Conflicts of interest in the evaluation of hyaluronic acid injections for osteoarthritis of the knee	48	RCT	None of the studies with a reported financial conflict of interest of at least one author had an unfavorable conclusion; 11 (35%) of the 31 studies with no industry-affiliated authors indicated that hyaluronic acid injection for knee osteoarthritis was no more effective than a placebo injection.
López <i>et al.</i> ³⁸ 2015	Association between funding and findings in plastic surgery	568	119 cohort studies, 3 cross-sectional studies, 39 case-controls, 22 RCTs, 256 case series and 129 conducted under another design.	Investigators with a financial conflict of interest are significantly more likely to publish plastic surgery studies with a positive conclusion compared with investigators with no conflicts of interest.
Lee <i>et al.</i> ³⁹ 2012	Thromboprophylaxis after total joint arthroplasty	66	53 prospective studies with a comparison group and 13 without a comparison group	Most studies on thromboprophylaxis after total joint arthroplasty are sponsored by the industry. Moreover, the qualitative conclusions in those studies are favorable to the use of the sponsored prophylactic agent.

RCT: randomized clinical trial

Source: Own elaboration.

Patient-oriented research

The search yielded 3 reviews that assess conflict of interest from the patients' perspective (Table 4). The first study reviews websites that describe payments to

physicians, analyzes them, and makes recommendations for improvement; the second concludes that, for patients, conflicts of interest do not appear to be important, and the third evaluates conflict of interest in

the development of tools designed to help people participate in decision-making about health care options and makes recommendations about various methods of presenting information about conflict of interest.

Table 4. Systematic reviews and meta-analyses on conflict of interest in patient-oriented research.

Authors	Assessment	Number of studies	Type of studies	Conclusions
Hwong <i>et al.</i> ⁴⁰ 2014	Websites that present data on payments to doctors.	21	List of ProPublica's disclosure websites (www.propublica.org), court investigation orders and public disclosure announcements	The development of a national disclosure website is only the first step to ensure transparency in physician-industry interactions. A central location for payment would allow more rigorous research into the effects of industry payments on patient care and the medical profession.
Fadlallah <i>et al.</i> ⁴¹ 2016	Patients and general public.	20	15 convenience sampling studies, 2 stratified random sampling studies, 1 systematic random sampling study, 1 simple random sampling study and 1 cluster random sampling study	Regarding physicians' receipt of personal gifts, awareness of participants and the general public was low. However, participants also reported greater acceptability and fewer perceived influence for office-use gifts compared to personal gifts.
Barry <i>et al.</i> ⁴² 2013	Support to patient decisions.	4	Meta-analysis	Disclosure of the conflict of interest alone is not sufficient, so it is recommended that the source of funding be disclosed in plain language.

Source: Own elaboration.

Discussion

Conflicts of interest can occur in any professional activity.⁴³ In medicine, for example, one of the areas in which conflict of interest and outcome bias can have the greatest impact is research, because the results of a biased study can put a large number of people at risk.⁴⁴

Even though there are different methodological procedures to reduce conflicts of interest (e.g. Cochrane's), these strategies focus on study design and development rather than on funding sources.⁴⁴ This is a serious problem since many researches around the globe are financed by the industry; in fact, this is the most common source of funding in the USA.⁴⁵

Some of the analyzed systematic reviews and meta-analyses report a tendency to favor the sponsoring entity.^{15-17,19} For instance, Bekelman *et al.*¹⁵ found that clinical trials funded by the drug manufacturer or in which the researchers have financial relationships with the manufacturers are 3.6 times more likely to report that the drug tested is effective compared to studies without such relationships.

There is also a low level of disclosure of conflicts of interest in CPGs, as the groups that develop them often do not make public their policies on the subject, their sources of funding for the development of guidelines, or the financial relationships of the members of the drafting panel. This lack of transparency makes it difficult for readers and users of the guidelines to assess undue influence and bias and, according to several studies, numerous conflicts of interest are evident when information is disseminated.²³⁻²⁷ However, it is necessary to highlight the effort made by some groups or entities developing CPGs to reduce the possibility of developers having conflicts of interest. This is an effort in which transparency (understood as a way of operating

so that the public can see clearly what actions are carried out) and accessibility have been cited as the most important aspects to assess conflict of interest policies in health organizations.⁴⁶

The conclusions of the clinical practice-based reviews presented in Table 3 showed that most found an association between the sponsored product and favorable research outcomes. Thus, in the review by Riaz *et al.*,³⁶ the declaration of financial conflicts of interest by at least one investigator was associated with a significantly higher probability of favorable outcomes for the drug or intervention under investigation ($p < 0.005$). On the other hand, DeGeorge *et al.*³³ found that studies that report conflict of interest are more likely to show a favorable outcome regarding infections ($p < 0.01$), wound complications ($p < 0.01$), overall morbidity ($p < 0.07$) and mortality ($p < 0.05$).³³

Finally, the review by Fadlallah *et al.*⁴¹ showed that patients and the general public care very little about the personal gifts their physicians receive from the pharmaceutical industry, and that when studies focus on surgeons, patients believe that professionals decide what is best for their health, regardless of their financial relationship with the industry.

Relationships between physicians and the industry are common and vary according to the specialty, type of practice and professional activity.⁴⁷ In the USA, of 850 000 active physicians, 616 567 received some type of payment in 2015⁴⁸ (average payment per physician: USD 3 242; median payment per physician: \$157); of these, 589 042 received food and drinks,¹ which was associated with a greater tendency to prescribe brand name drugs, even when there are equally effective generic drugs.⁴⁸⁻⁵³

In all medical activities, it is important to establish policies that reduce the influence of secondary interests,

clearly communicate the financial link with the industry, prohibit the acceptance of gifts or entertainment, and seek alternatives to industry funding of continuing medical education activities.^{54,55} Careful policy setting regarding conflicts of interest helps maintain confidence in academics.⁵⁶

The relationship between the industry and researchers has been the subject of intense debate worldwide. Such is the case of the organization Cochrane, a very respected organization in the academic field, and the studies on the effectiveness and safety of the human papillomavirus vaccine, which have been at the center of controversy due to the quality of the review conducted by Arbyn *et al.*,⁵⁷ the sponsorship of these studies,⁵⁸ and the existing conflict of interests of the reviewers.⁵⁹

The main limitation of the present review is that the search was conducted only in two databases, had broad inclusion criteria and its findings were descriptive.

Conclusions

There are relationships between the pharmaceutical industry and physicians that can affect professional practice since interests, different from clinical research, may arise.

The publications analyzed in this review showed that the original studies included in the systematic reviews and meta-analyses do not always report conflicts of interest. However, when they are mentioned, the results tend to favor the sponsor's drug or device.

Conflicts of interest

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