Reporting of Conflicts of Interest in Meta-analyses of Trials of Pharmacological Treatments

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Context Disclosure of conflicts of interest (COIs) from pharmaceutical industry study funding and author-industry financial relationships is sometimes recommended for randomized controlled trials (RCTs) published in biomedical journals. Authors of meta-analyses, however, are not required to report COIs disclosed in original reports of included RCTs.

Objective To investigate whether meta-analyses of pharmacological treatments published in high-impact biomedical journals report COIs disclosed in included RCTs.

Data Sources and Study Selection We selected the 3 most recent meta-analyses of patented pharmacological treatments published January 2009 through October 2009 in each general medicine journal with an impact factor of at least 10; in high-impact journals in each of the 5 specialty medicine areas with the greatest 2008 global therapeutic sales (oncology, cardiology, respiratory medicine, endocrinology, and gastroenterology); and in the Cochrane Database of Systematic Reviews.

Data Extraction Two investigators independently extracted data on disclosed study funding, author-industry financial ties, and author employment from each meta-analysis, from RCTs included in each meta-analysis, and on whether meta-analyses reported disclosed COIs of included RCTs.

Results Of 29 meta-analyses reviewed, which included 509 RCTs, only 2 meta-analyses (7%) reported RCT funding sources; and 0 reported RCT author-industry ties or employment by the pharmaceutical industry. Of 318 meta-analyzed RCTs that reported funding sources, 219 (69%) were industry funded; and 91 of 132 (69%) that reported author financial disclosures had 1 or more authors with pharmaceutical industry financial ties. In 7 of the 29 meta-analyses reviewed, 100% of included RCTs had at least 1 form of disclosed COI (pharmaceutical industry funding, author-industry financial ties, or employment), yet only 1 of these 7 meta-analyses reported RCT funding sources, and 0 reported RCT author-industry ties or employment.

Conclusion Among a group of meta-analyses of pharmacological treatments published in high-impact biomedical journals, information concerning primary study funding and author COIs for the included RCTs were only rarely reported.

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Conflicts of interest (COIs) related to the funding of biomedical research by pharmaceutical companies and financial relationships between researchers and pharmaceutical companies have come under increased scrutiny in recent years.[1-3] COIs may influence the framing of research questions, study design, data analysis, interpretation of findings, whether to publish results, and what results are reported.[4,5] Results from positive trials and from favorable analyses are more likely to be published than results unfavorable to sponsors.[6-8] Compared with nonindustry-funded trials, pharmaceutical industry–funded studies more often yield results or conclusions in support of the sponsor's drug,[9-16] and authors' relationships with drug manufacturers have been linked to favorable assessments of drug efficacy and safety.[17-20]

As a result, increased emphasis has been placed on the transparent disclosure of COI. The Consolidated Standards of Reporting Trials (CONSORT) guidelines require disclosure of study funding sources in trial reports.[21,22] International Committee of Medical Jour-

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nal Editors (ICMJE) guidelines recommend disclosure by authors of study funding sources and also of author-industry financial ties.[23] There are no guidelines, however, for the reporting in meta-analyses of COIs disclosed in included randomized controlled trials (RCTs). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement requires meta-analysis authors to report the funding source of a meta-analysis, but does not address the reporting of COI from included RCTs.[24,25] Meta-analyses are cited more than any other study design[26] and prioritized in grading evidence for practice guidelines.[27] Meta-analyses supported by the pharmaceutical industry, through study funding or author-industry financial ties, more often reach conclusions that favor sponsors' interests than meta-analyses not linked to industry.[28-30] Without documentation in meta-analyses of COIs from included RCTs, users of meta-analyses may not have access to important information that could influence their evaluation of the risk of bias in the evidence reported.

The objective of this study was to investigate the extent to which pharmaceutical industry funding and author-industry financial ties or author employment disclosed in published reports of RCTs of pharmacological interventions are transparently reported in meta-analyses published in high-impact general and specialty medicine journals and the Cochrane Database of Systematic Reviews. We hypothesized that few meta-analyses would report COIs disclosed in original reports of included RCTs.

METHODS

Meta-analysis Selection

We selected a sample of meta-analyses published from January 2009 through October 2009 in 3 categories of high-impact publications: (1) general medicine journals, (2) journals representing the top 5 specialty medicine areas based on 2008 global pharmaceutical sales (oncology, cardiology, respiratory medicine, endocrinology, and gastroenterology),[31] and (3) the Cochrane Database of Systematic Reviews. We prioritized recently published meta-analyses to reflect current reporting practices because standards are evolving.[23,24]

Within general medicine journals, we selected the 3 most recently published eligible meta-analyses from each journal with a 2008 impact factor of at least 10 (*New England Journal of Medicine, JAMA, Lancet, BMJ, Annals of Internal Medicine, PLoS Medicine*),[32] with fewer included if there were not 3 that met eligibility criteria. Within each specialty medicine area, we also identified 3 recently published meta-analyses. We started with the most recently published meta-analyses in the top impact factor journal[32] in each specialty area, then searched the second highest-rated journal if 3 eligible meta-analyses were not published in the top journal, and continued to search journals in declining order of impact factor until 3 eligible meta-analyses were obtained.

To obtain our sample, we searched the MEDLINE database via PubMed using limits of article type (*meta-analysis*) with journal names, supplemented by a manual search of each journal's table of contents for the term *meta-analysis* in article titles or abstracts. For articles published in the same journal issue, the article with the highest page number was considered most recent. Articles published online ahead of print as of October 31, 2009, were not eligible. In addition, meta-analyses from the most recent Cochrane Database of Systematic Reviews issue (issue 4, 2009) were selected for review based on random numbers generated in Microsoft Excel until 3 eligible meta-analyses were obtained.

Eligibility Criteria

Eligible meta-analyses (1) included a documented systematic review of the literature, (2) statistically combined results from at least 2 RCTs, (3) did not include non-RCTs, (4) evaluated the efficacy or harm of a drug or class of drug against an alternative treatment (eg, placebo, alternative drug), and (5) included at least 1 drug in the intervention or comparison study groups that was under patent in the United States at the time of publication based on the electronic US Food and Drug Administration Orange Book.[33] A drug was classified as under patent if any aspect of the active ingredient (eg, dosage, route, strength) was protected by an unexpired patent. We selected meta-analyses with at least 1 drug under patent in order to restrict the sample to drugs of potentially high economic importance to pharmaceutical companies. Meta-analyses that investigated biologics or that investigated a combination of pharmacological and nonpharmacological interventions (eg, psychotherapy) were included if a drug intervention alone was assessed as a study group.

If either of 2 reviewers independently deemed a retrieved meta-analysis to be potentially eligible based on title and abstract review, then a full-text review was conducted. Full-text reviews were conducted independently by 2 reviewers, 1 meta-analysis at a time in reverse temporal sequence until 3 eligible articles were obtained from each general medicine journal, each specialty medicine area, and the Cochrane Database of Systematic Reviews. Chance-corrected agreement between reviewers was assessed with the Cohen κ statistic with any disagreements resolved by consensus. Translators assisted reviewers to evaluate non-English titles, abstracts and articles and in data extraction.

Data Extraction

Two investigators independently reviewed all meta-analyses and included RCTs, including disclosure statements, article texts and tables, author bylines and acknowledgments, and all online journal supplements (see eAppendix for data extraction forms at http://www.jama.com) to identify (1) disclosure of COIs (study funding, author-industry financial ties or employment) from each selected meta-analysis; (2) disclosure of COIs for all

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RCTs included in each meta-analysis; and (3) to determine whether or not disclosed COIs from included RCTs were reported in meta-analyses. For included RCTs published only as abstracts, we verified whether a separate disclosure section was published and extracted data, as appropriate. For meta-analyses, we also determined whether a quality or risk of bias assessment of included RCTs was conducted and, if so, the instrument used.

Study funding sources for meta-analyses and included RCTs were classified as pharmaceutical industry, nonindustry (eg, public granting agency, private not-for-profit granting agency), combined pharmaceutical industry and nonindustry, nonindustry with drug supplied by pharmaceutical industry (RCTs only), no study funding, or not reported. Studies reported as funded "in part" by the pharmaceutical industry with no other indication of funding source were coded as industry-funded. Study funding included provision of financial support, resources (eg, statistical analyses), or inclusion of study personnel beyond those listed as authors.

Author financial ties to industry were defined per the October 2009 version of the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest[23] and included current or former board membership, current or former consultancy, former industry employment, equity holdings (eg, stock, stock options), expert testimony, gifts, patents (planned, pending, or issued), payment for manuscript preparation, other research funding, royalties, speaker fees/payment for presentation development, travel reimbursement, or unspecified honoraria, as disclosed in the article. If an article did not contain a disclosure statement or acknowledgments, author-industry financial ties were coded as not reported. Authorship by individuals employed by the pharmaceutical industry at the time of article publication was coded separately as industry employment.

If a meta-analysis included citations to multiple articles reporting on the same RCT, each article was reviewed and COIs were coded as present if reported in any of the cited articles. For meta-analyses that included RCTs of both pharmacological and nonpharmacological interventions, only RCTs that assessed a pharmacological intervention alone as a study group were reviewed. Any discrepancies in data extraction were resolved by consensus.

Corresponding authors of meta-analyses were contacted via e-mail (as many as 3 attempts) to determine whether data extraction protocols included study funding and author-industry financial ties.

RESULTS

Search Results

A total of 133 potentially eligible titles/abstracts were reviewed, including 52 from general medicine journals, 70 from specialty medicine journals, and 11 from the Cochrane Database of Systematic Reviews. Of these, 93 were excluded after title/abstract review and 11 after full-text review, leaving 29 eligible meta-analyses that were included in the review (eTable 1).[34-62] The 29 meta-analyses included 11 from general medicine journals (3 each from *JAMA, Lancet*, and *BMJ;* 2 from *Annals of Internal Medicine*; 0 from *New England Journal of Medicine* or *PLoS Medicine)*, 15 from specialty medicine journals, and 3 from the Cochrane Database of Systematic Reviews. Impact factors of journals with included meta-analyses ranged from 12.2 to 31.7 in general medicine, 13.3 to 17.2 in oncology, 8.9 to 14.6 in cardiology, 5.2 to 5.5 in respiratory medicine, 6.4 to 7.3 in endocrinology, 7.4 to 9.8 in gastroenterology, and 5.2 for the Cochrane Database of Systematic Reviews. Cohen κ for chance-corrected agreement on inclusion/exclusion decisions was 0.94.

As shown in TABLE 1 and TABLE 2, the 29 selected meta-analyses evaluated a broad spectrum of pharmacological interventions, including 21 on treatment efficacy, 3 on harms, and 5 on both efficacy and harms. Between 2 and 65 RCTs were included in each meta-analysis.

Study Funding and Author-Industry Financial Ties of Meta-analyses

As shown in Table 1 and Table 2, 0 of the 29 selected meta-analyses reported being funded by the pharmaceutical industry. Fourteen (48.3%) reported nonindustry funding, 4 reported no study funding (13.8%), and the funding source of 11 (37.9%) was not reported. At least 1 author of 16 of the 29 meta-analyses (55.2%) reported at least 1 financial tie to the pharmaceutical industry, all of the authors of 12 of the meta-analyses (41.4%) reported 0 financial ties to the pharmaceutical industry, and author financial ties were not reported in 1 meta-analysis (3.4%). Specific types of author ties to the pharmaceutical industry for each meta-analysis are shown in eTable 2. Only 1 of the 29 meta-analyses listed authors employed by the pharmaceutical industry.[37]

Study Funding and Author-Industry Financial Ties of Included RCTs

The 29 selected meta-analyses synthesized data from a total of 509 RCTs. As shown in TABLE 3, 62.5% (318 of 509) of included RCTs reported funding source. Of these, 68.9% (219 of 318) were funded in part or whole by the pharmaceutical industry; 30.5% (97 of 318) by nonindustry funding sources, including 28 RCTs in which a study drug was supplied by the pharmaceutical industry; and less than 1% (2 of 318) reported that the trial received no funding. Characteristics of the 509 included RCTs, including COI data, are presented in eTable 3.

Author financial disclosures were reported in only 25.9% (132 of 509) of included RCTs. Among these, 68.9% (91 of 132) reported 1 or more authors having financial ties to the pharmaceutical industry. Author affiliations were reported in 94.7% of included RCTs (482 of 509), including 26.1% (126 of 482) with at least 1 author employed by the pharmaceutical industry.

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Reporting of Disclosed COIs From RCTs Included in Meta-analyses

As shown in Table 3, only 2 of the 29 selected meta-analyses reported the funding source of included RCTs.[47,62] One listed RCT funding sources in a table footnote[47] and the other in the Characteristics of Studies table that followed the main document and references.[62] Neither mentioned RCT funding sources in the column of a core table, in the text, or in an assessment of potential bias. Both of these meta-analyses[47,62] reported nonindustry funding for the meta-analysis. One of the meta-analyses reported no author ties to the pharmaceutical industry,[62] whereas the other reported that 1 of 3 authors had a link to the pharmaceutical industry.[47] None of the 29 meta-analyses reported author-industry financial ties or employment of included RCTs.

Of the 29 meta-analyses, 25 assessed quality or risk of bias in included RCTs. One of the meta-analyses that reported the funding source of included RCTs[47] used an ad hoc method to assess study quality that did not include an assessment of study funding. Five meta-analyses[34,44,60-62] used at least 3 of the 6 domains from the Cochrane Risk of Bias tool, which does not produce a single quality score, but rather provides ratings for individual risk components.[63] Only 1 of the 5 meta-analyses[62] reported the funding source of included RCTs, but it did not include this information in the assessment of risk of bias.

In 7 of 29 meta-analyses (Table 3), 100% of included RCTs disclosed at least 1 form of COI in the original RCT publications.[37,38,40,44,47,54,60] In 4 of these 7 meta-analyses,[37,44,54,60] 100% of included RCTs that reported study funding were funded by the pharmaceutical industry. Only 1 of the 7 meta-analyses, however, provided information on study funding of included RCTs,[47] and that was done in a table footnote.

Twenty-seven of 29 meta-analysis authors provided information on data extraction protocols. Two recorded and reported RCT funding sources[47,62]; 5 recorded, but did not report funding sources; and 20 did not record funding sources. Only 2 of the 27 meta-

Table 1. Characteristics of Included Meta-analyses in General Medicine Journals

Source, Journal (Review Date Range)[a]	No. of RCTs in Meta-analysis	No. of Articles Reviewed	Diagnosis	Comparison Measures: Intervention	Comparison Measures: Group	Comparison Measures: Outcome	Funding Source	Meta-analysis Authors, No.[b]: With Industry Financial Ties/ Total in Meta-analysis	Meta-analysis Authors, No.[b]: With Industry Employment/ Total in Meta-analysis
de Almeida, *JAMA* (1976-2008)[34]	18	18	Bell palsy	Corticosteroids, antivirals, or both	Placebo or control	Efficacy	Nonindustry	1/7	0/7
Berger, *JAMA* (1975-2008)[35]	18	18	PAD	Aspirin (with or without dipyridamole)[c]	Placebo or control	Efficacy	None	3/4	0/4
Häuser, *JAMA* (1986-2008)[36]	18	18	FMS	Antidepressants	Placebo	Efficacy	Nonindustry	3/4	0/4
Sin, *Lancet* (1998-2009)[37]	7	7	COPD	Budesonide (with or without formoterol)	Placebo or control	Harm	Nonindustry	7/8	3/8
Ray, *Lancet* (1998-2009)[38]	5	9	Type 2 DM	Intensive glucose-lowering regimens	Standard glucose-lowering regimens	Efficacy	None	2/8	0/8
Heerspink, *Lancet* (2003-2008)[39]	8	8	Maintenance dialysis	Blood pressure–lowering treatment	Placebo or control	Efficacy	Nonindustry	0/11	0/11
Kelly, *Ann Intern Med* (1998-2009)[40]	5	5	Type 2 DM	Intensive glucose control	Conventional glucose control	Efficacy and harm	Nonindustry	0/6	0/6
Fuccio, *Ann Intern Med* (2000-2008)[41]	7	7	*H pylori* positive	*H pylori* eradication treatment	Placebo or control	Efficacy	Not reported	0/8	0/8
Quant, *BMJ* (1996-2008)[42]	6	6	Bell palsy	Steroids plus antivirals	Steroids	Efficacy	None	1/6	0/6
Hayward, *BMJ* (1993-2008)[43]	8	8	Sore throat[d]	Corticosteroids	Placebo or control	Efficacy	Nonindustry	0/6	0/6
Shun-Shin, *BMJ* (2000-2006)[44]	7	7	Seasonal influenza[e]	Neuraminidase inhibitors	Placebo or control	Efficacy	None	0/6	0/6

Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FMS, fibromyalgia syndrome; PAD, peripheral artery disease.
[a] All included meta-analyses were published in 2009; review date range indicates the publication dates of articles reviewed for each meta-analysis.
[b] Details of author-industry financial ties and pharmaceutical author industry employment are provided in eTable 2.
[c] A combined formulation of aspirin and dipyridamole was under patent.
[d] Study included adults and children.
[e] Study included only children.

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analyses recorded RCT author-industry financial ties, but neither published this information.

COMMENT

The main finding of this study is that with few exceptions, information on COI disclosed in RCTs is not reported when RCT data are combined in meta-analyses. Pharmaceutical industry fund-

Table 2. Characteristics of Included Meta-analyses in Specialty Medicine Journals and the Cochrane Database of Systematic Reviews

Source, Journal (Review Date Range)[a]	No. of RCTs in Meta-analysis	No. of Articles Reviewed	Diagnosis	Comparison Measure: Intervention	Comparison Measure: Group	Comparison Measure: Outcome	Funding Source	Meta-analysis Authors, No.[b]: With Industry Financial Ties/ Total in Meta-analysis	Meta-analysis Authors, No.[b]: With Industry Employment/ Total in Meta-analysis
Oncology									
Soon, *J Clin Oncol* (1989-2008)[45]	13	13	Advanced NSCLC	Extended chemotherapy	Standard duration chemotherapy	Efficacy	Not reported	1/4	0/4
Di Maio, *J Clin Oncol* (2004-2009)[46]	6	6	Advanced NSCLC	Doublet chemotherapy, second line	Single-agent chemotherapy, second line	Efficacy	Not reported	4/12	0/12
Hapani, *Lancet Oncol* (2004-2008)[47]	17	17	Cancer	Bevacizumab	Placebo or control[c]	Harm	Nonindustry	1/3	0/3
Cardiology									
Ho and Tan, *Circulation* (1977-2008)[48]	50	50	Cardiac surgery	Corticosteroid prophylaxis	Placebo or control	Efficacy	Nonindustry	0/2	0/2
De Luca, *J Am Coll Cardiol* (2004-2008)[49]	6	6	STEMI, primary angioplasty	Abciximab	Small molecule antiplatelet drugs	Efficacy	Not reported	1/4	0/4
Verdecchia, *Eur Heart J* (1996-2008)[50]	31	31	HTN or high cardio-vascular risk	New anti-hypertensive drugs	Old anti-hypertensive drugs	Efficacy	Nonindustry	4/7	0/7
Respiratory Medicine									
Wijesinghe, *Eur Respir J* (1991-2007)[51]	62[d]	59	Asthma	Formoterol	Placebo or non-LABA drug	Harm	Nonindustry	1/5	0/5
Sindi, *Chest* (1994-2006)[52]	32	32	Asthma[e]	(1) LABAs (2) LABA plus ICS	(1) Placebo (2) ICS alone	Efficacy	Not reported	0/3	0/3
Tassinari, *Chest* (2000-2007)[53]	14	14	Advanced NSCLC	(1) Any second-line antineoplastic treatment (2) Docetaxel	(1) Placebo or control (2) Other second-line antineoplastic treatment	Efficacy	Not reported	0/7	0/7
Endocrinology									
Rajpathak, *Diabetes Care* (2001-2008)[54]	6	6	Primary and secondary cardiovascular prevention trials	Statins	Placebo	Efficacy and harm	Nonindustry	1/6	0/6
Hartweg, *Curr Opin Lipidol* (1988-2008)[55]	29[f]	41	Type 2 DM	Omega-3 PUFAs	Placebo or control	Efficacy	Not reported	Not reported/4	0/4
Lasserson, *Diabetologia* (1991-2008)[56]	22	22	Type 2 DM	Insulin regimens (basal, prandial, biphasic)	Alternate insulin regimen	Efficacy and harm	Not reported	1/5	0/5
Gastroenterology									
Ford, *Gut* (1978-2008)[57]	13[g]	13	IBS	Antidepressants	Placebo	Efficacy	Nonindustry	4/5	0/5
Ravipati, *Gastrointest Endosc* (1988-2006)[58]	12[h]	12	Previous esophageal variceal bleeding	Pharmacotherapy (β-blockers, nitrates)	Endoscopic therapy	Efficacy	Not reported	0/5	0/5
Barkun, *Gastrointest Endosc* (1990-2004)[59]	19[i]	18[j]	High-risk peptic ulcers	Pharmacotherapy	Endoscopic therapy	Efficacy	Not reported	1/5	0/5

(continued)

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Table 2. Characteristics of Included Meta-analyses in Specialty Medicine Journals and the Cochrane Database of Systematic Reviews (continued)

Source, Journal (Review Date Range)[a]	No. of RCTs in Meta-analysis	No. of Articles Reviewed	Diagnosis	Comparison Measure: Intervention	Comparison Measure: Group	Comparison Measure: Outcome	Funding Source	Meta-analysis Authors, No.[b]: With Industry Financial Ties/ Total in Meta-analysis	Meta-analysis Authors, No.[b]: With Industry Employment/ Total in Meta-analysis
Cochrane Database of Systematic Reviews									
Caslake, Cochrane Database Syst Rev (1992-2001)[60]	2	6	Early Parkinson disease	MAO-B inhibitors	Alternative dopaminergic agents	Efficacy and harm	Nonindustry	0/5	0/5
Koch and Polman, Cochrane Database Syst Rev (2000-2007)[61]	3	3	Partial onset seizures[e]	Oxcarbazepine	Carbamazepine	Efficacy and harm	Not reported	0/2	0/2
Perez, Cochrane Database Syst Rev (1966-2008)[62]	65	100[k]	Acute cardiovascular events	Antihypertensive drugs	Placebo or control	Efficacy	Nonindustry	0/3	0/3

Abbreviations: DM, diabetes mellitus; HTN, hypertension; IBS, irritable bowel syndrome; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; MAO-B, monoamine oxidase B; NSCLC, non-small cell lung cancer; PUFA, polyunsaturated fatty acid; STEMI, ST-segment elevation myocardial infarction.
[a] All included meta-analyses were published in 2009; review date range indicates the publication dates of articles reviewed for each meta-analysis.
[b] Details of author-industry financial ties and pharmaceutical author industry employment are provided in eTable 2.
[c] Comparison arm (control chemotherapy treatment) included patented drug.
[d] Fifty-nine citations reported the results of 62 RCTs (3 citations each reported the results of 2 RCTs).
[e] Study included adults and children.
[f] Meta-analysis reported that 30 RCTs were included. However, 1 RCT was listed twice.
[g] Meta-analysis included 32 RCTs in total, of which 13 were RCTs of pharmacological interventions and 19 were RCTs of psychological treatments.
[h] Meta-analysis included 26 RCTs in total, of which 12 were RCTs of pharmacotherapy alone vs endoscopic therapy and 14 were RCTs of pharmacotherapy plus endoscopic therapy vs endoscopic therapy and did not assess the pharmacological intervention alone.
[i] Meta-analysis included 42 RCTs in total, of which 19 were RCTs of pharmacotherapy alone vs endoscopic therapy and 23 were RCTs that compared endoscopic therapies.
[j] Eighteen citations reported the results of 19 RCTs (1 citation reported the results of 2 RCTs).
[k] Meta-analysis reference list included 103 citations. However, 3 included citations were each listed twice in reference list.

ing was present in 69% of the RCTs that disclosed funding. However, only 2 of 29 meta-analyses provided information on funding sources of included RCTs. None reported author-industry financial ties or employment disclosed in the original RCT publications. The 2 meta-analyses that reported RCT funding sources provided this information in a table that followed the main document and references[62] and in a table footnote,[47] neither of which are typically reviewed by the average reader. Neither meta-analysis described sources of COIs in a core table, in the text, or in an analysis of potential sources of bias.

There is general agreement on the need for complete and transparent disclosure of COI in biomedical research.[21-23] The results of the present study highlight a major gap in the reporting of COIs and suggest that, without a formal reporting policy, COIs from RCTs are unlikely to be reported when results are synthesized in meta-analyses. The PRISMA statement should be updated to require authors of meta-analyses to report funding sources of included RCTs or report that funding sources were not disclosed. Study funding was disclosed in the original reports of approximately two-thirds of RCTs in this review.

In addition to information on study funding, consumers of research, including patients and physicians, want researcher financial ties to industry to be disclosed[64] and consider author-industry financial ties in assessing the quality of research evidence.[64-66] The authors of the PRISMA statement should also consider recommending that meta-analyses report author-industry financial ties disclosed in included RCTs or report that there was no disclosure statement. Although author-industry ties are less frequently reported than study funding sources in published reports of RCTs included in meta-analyses, the proportion of RCTs reporting author-industry financial ties will likely increase with the recent introduction of ICMJE disclosure guidelines. The nature and extent of author-industry ties disclosed in RCTs are complex. However, coding the proportion of authors with disclosed industry financial ties would not be a great burden and would flag studies with COIs from author-industry financial ties for interested readers.

Authors of meta-analyses are expected to transparently assess and interpret potential sources of bias from included studies that could influence outcomes. Items included in quality or risk of bias assessment tools (eg, sequence generation, blinding) are increasingly selected based on empirical evidence of an association with bias, including the mechanism, direction, and likely magnitude of possible bias.[63,67] Meta-analysis authors should document that they have evaluated all potentially relevant sources of bias, whether or not a particular source of possible bias is present in the studies reviewed and whether or not the magnitude of bias is expected to be large in comparison with

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Table 3. Disclosure and Reporting in Meta-analyses of RCT Funding Source, Author Financial Ties to the Pharmaceutical Industry, and Author Employment by the Pharmaceutical Industry

				No. of RCTs							
		RCT Data Reported in Meta-analysis		Funding Source		Author Financial Disclosure		Author Affiliation			
Source, Journal	No. of Included RCTs	Industry Funding	Author-Industry Ties/ Employment	Reported[a]	With Industry Support[b]	Reported[a]	With Industry Ties[b]	Reported[a]	With Industry Employment[b]	With Industry Funding or Author-Industry Ties/ Employment[a]	Meta-analysis Quality Assessment[c]
de Almeida, *JAMA*[34]	18	No	No	6/18	2/6	2/18	2/2	17/18	0/17	3/18	Cochrane
Berger, *JAMA*[35]	18	No	No	9/18	5/9	2/18	0/2	15/18	3/15	7/18	Jadad
Häuser, *JAMA*[36]	18	No	No	12/18	9/12	3/18	3/3	18/18	8/18	13/18	Jadad, Van Tulder
Sin, *Lancet*[37]	7	No	No	6/7	6/6	3/7	2/3	7/7	6/7	7/7	Jadad
Ray, *Lancet*[38]	5	No	No	5/5	4/5	4/5	4/4	4/5	1/4	5/5	None
Heerspink, *Lancet*[39]	8	No	No	4/8	3/4	4/8	0/4	8/8	2/8	5/8	Jadad, ad hoc
Kelly, *Ann Intern Med*[40]	5	No	No	5/5	4/5	3/5	3/3	3/5	0/3	5/5	Ad hoc
Fuccio, *Ann Intern Med*[41]	7	No	No	5/7	0/5	1/7	0/1	5/7	0/5	0/7	Ad hoc
Quant, *BMJ*[42]	6	No	No	4/6	2/4	3/6	2/3	6/6	0/6	3/6	Jadad
Hayward, *BMJ*[43]	8	No	No	1/8	0/1	1/8	0/1	8/8	0/8	0/8	Ad hoc
Shun Shin, *BMJ*[44]	7	No	No	7/7	7/7	3/7	3/3	6/7	6/6	7/7	Cochrane
Soon, *J Clin Oncol*[45]	13	No	No	6/13	4/6	3/13	1/3	12/13	2/12	6/13	Ad hoc
Di Maio, *J Clin Oncol*[46]	6	No	No	4/6	1/4	2/6	0/2	6/6	0/6	1/6	MERGE checklist
Hapani, *Lancet Oncol*[47]	17	Yes	No	12/17	9/12	17/17	16/17	17/17	9/17	17/17	Ad hoc
Ho and Tan, *Circulation*[48]	50	No	No	19/50	4/19	6/50	0/6	50/50	0/50	4/50	Ad hoc
De Luca, *J Am Coll Cardiol*[49]	6	No	No	4/6	3/4	4/6	3/4	6/6	0/6	4/6	None
Verdecchia, *Eur Heart J*[50]	31	No	No	29/31	29/29	16/31	14/16	25/31	9/25	29/31	Jadad
Wijesinghe, *Eur Respir J*[51]	62	No	No	38/62	37/38	10/62	10/10	58/62	39/58	51/62	None
Sindi, *Chest*[52]	32	No	No	24/32	18/24	5/32	5/5	32/32	5/32	22/32	Jadad, ad hoc
Tassinari, *Chest*[53]	14	No	No	7/14	6/7	8/14	5/8	14/14	8/14	10/14	Nicolucci
Rajpathak, *Diabetes Care*[54]	6	No	No	6/6	6/6	6/6	6/6	5/6	1/5	6/6	Jadad
Hartweg, *Curr Opin Lipidol*[55]	29	No	No	20/29	8/20	8/29	2/8	29/29	1/29	9/29	Ad hoc
Lasserson, *Diabetologia*[56]	22	No	No	20/22	19/20	7/22	7/7	22/22	14/22	20/22	Jadad, ad hoc
Ford, *Gut*[57]	13	No	No	7/13	2/7	2/13	0/2	13/13	2/13	4/13	Jadad
Ravipati, *Gastrointest Endosc*[58]	12	No	No	5/12	0/5	1/12	1/1	12/12	0/12	1/12	None
Barkun, *Gastrointest Endosc*[59]	19	No	No	8/19	2/8	3/19	0/3	19/19	1/19	2/19	Ad hoc

(continued)

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Table 3. Disclosure and Reporting in Meta-analyses of RCT Funding Source, Author Financial Ties to the Pharmaceutical Industry, and Author Employment by the Pharmaceutical Industry (continued)

		RCT Data Reported in Meta-analysis		No. of RCTs							
				Funding Source		Author Financial Disclosure		Author Affiliation			
Source, Journal	No. of Included RCTs	Industry Funding	Author-Industry Ties/ Employment	Reported[a]	With Industry Support[b]	Reported[a]	With Industry Ties[b]	Reported[a]	With Industry Employment[b]	With Industry Funding or Author-Industry Ties/ Employment[a]	Meta-analysis Quality Assessment[c]
Caslake, *Cochrane Database Syst Rev*[60]	2	No	No	2/2	2/2	0/2	0/0	2/2	0/2	2/2	Cochrane[d]
Koch and Polman, *Cochrane Database Syst Rev*[61]	3	No	No	1/3	1/1	1/3	1/1	3/3	1/3	2/3	Cochrane[e]
Perez, *Cochrane Database Syst Rev*[62]	65	Yes	No	42/65	26/42	4/65	1/4	60/65	8/60	30/65	Cochrane
Totals, No. (%)	509	2/29 (7)	0/29 (0)	318/509 (63)	219/318 (69)	132/509 (26)	91/132 (69)	482/509 (95)	126/482 (26)	NA[f]	NA[f]

Abbreviations: NA, not applicable; RCT, randomized controlled trial.
[a] Numerator is the number of RCTs that reported; denominator is the number of RCTs in the meta-analysis.
[b] Numerator is the number of RCTs with conflict of interest; denominator is the number of RCTs that reported.
[c] Quality or risk of bias tool used by meta-analysis authors to assess included RCTs.
[d] Abridged version of Cochrane Risk of Bias tool, including only 4 of 6 domains.
[e] Abridged version of Cochrane Risk of Bias tool, including only 3 of 6 domains.
[f] It was not possible to report a combined proportion of trials reported since different numbers of meta-analyses provided different information for funding source, author financial ties, and author employment.

other likely sources of bias. Risk of bias ratings for various domains are used by meta-analysts as stratification factors in sensitivity analyses or more qualitatively. For instance, meta-analysts might note that all RCTs in a given review have significant design shortcomings and a high risk of bias.

COIs from pharmaceutical industry study funding and author-industry financial ties meet the empirical criteria typically used to select other potential sources of bias for inclusion in evidence quality and risk of bias assessment tools. Pharmaceutical industry funding and author-industry financial ties are associated with a bias toward favorable results even when controlling for other study characteristics.[12,13] Based on empirical evidence of bias related to COI, an Agency for Healthcare Research and Quality systematic review of tools used to rate evidence quality[67] included the category *funding or sponsorship* as a key evaluation domain and rated tools higher if they included an assessment of potential bias from industry sponsorship. Similarly, the recently developed Assessment of Multiple Systematic Reviews tool for grading the methodological quality of systematic reviews includes a score for whether COIs from included studies are clearly described.[68]

Meta-analysts should evaluate the potential for bias due to pharmaceutical industry study funding and author-industry financial ties as part of their standard risk of bias assessment. As with other potential sources of bias, results from this domain should be transparently documented and used in sensitivity analyses or qualitatively. For instance, a set of positive results from industry-funded trials would likely be interpreted with more confidence if corroborated by at least 1 study with similar findings that was not industry-funded. The funding source and thus the risk of bias due to industry funding will be unclear for some studies, such as those conducted prior to the adoption of guidelines for declaring this type of information.

Although some risk of bias assessment tools include a domain for study funding source, most do not.[67] Currently, the Cochrane Collaboration's Risk of Bias tool includes an optional "other sources of bias" domain,[63] which meta-analysts could use to include information on COIs. We recommend that the Cochrane Collaboration consider formalizing the requirement to assess potential bias from COIs.

Several limitations should be considered in interpreting results from this study. First, the study was not designed to assess whether reporting of COI from RCTs included in meta-analyses was related to the quality of meta-analyses or whether COIs from included RCTs influenced the results of the meta-analyses reviewed. However, the motivation to conduct this study was based on extensive research that has shown that COIs can influence the results and conclusions of both RCTs and meta-analyses.[11,13,14,28-30] Second, we reviewed a relatively small sample of meta-analyses from high-impact journals, and it is not clear to what degree these results can be generalized to other areas of medicine or to lower-impact journals. None of the 29 meta-analyses reviewed reported funding from the pharmaceu-

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tical industry, for instance, and it is possible that we undersampled industry-funded meta-analyses. However, given that only 2 of 29 (7%) meta-analyses mentioned COIs from included RCTs, it is likely that the main findings of the study are generalizable. Finally, the exact nature of COIs in included RCTs (eg, amount of industry funding, role of funding source) was not assessed. However, this information is not typically available and studies that have identified links between pharmaceutical industry funding and study outcomes have similarly relied upon dichotomous coding.[10,12,15,16]

In summary, this study found that meta-analyses of pharmacological interventions published in high-impact medical journals rarely reported the funding sources or author-industry financial ties of included RCTs, even when these sources of COIs were disclosed in RCT reports. PRISMA should require the reporting of study funding sources and author-industry financial ties of RCTs in meta-analyses, and this information should be included in risk of bias assessments.

Risk of bias assessment in meta-analyses due to COI or other sources of potential bias in included RCTs is imperfect, and disclosure is a necessary first step, but not sufficient to mitigate the effects of COI on biomedical research.[69] Nonetheless, if COIs disclosed by authors of RCTs are not reported when RCTs are synthesized in meta-analyses, efforts to achieve greater transparency in biomedical research through disclosure requirements may be less effective. Given that COIs are prominent in biomedical research and have been empirically linked to bias, it is the responsibility of authors of meta-analyses to transparently document for readers their efforts to evaluate the likely influence of COI on meta-analysis outcomes.

If COIs from included RCTs are not acknowledged in meta-analyses, 1 of 2 messages may be sent to readers—the first is that the authors of the meta-analysis have not considered COI in included studies, which leaves readers in a position of not knowing how to interpret possible biases that may have arisen because of COI in the original RCTs; and the second possible message is that the meta-analysts have in fact assessed the risk of bias related to COI in the original RCTs, concluded that the COIs did not create any biases, and therefore have chosen not to comment on the COIs. This interpretation may lead readers to trust the conclusions of a meta-analysis when they potentially should not. In either case, without acknowledgment of COI due to industry funding or author-industry financial ties from RCTs included in meta-analyses, readers' understanding and appraisal of the evidence from the meta-analysis may be compromised.

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Study concept and design: Roseman, Milette, Bero, Coyne, Lexchin, Turner, Thombs.
Acquisition of data: Roseman, Milette, Thombs.
Analysis and interpretation of data: Roseman, Milette, Bero, Coyne, Lexchin, Turner, Thombs.
Drafting of manuscript: Roseman, Thombs.
Critical revision of manuscript for important intellectual content: Roseman, Milette, Bero, Coyne, Lexchin, Turner, Thombs.
Statistical analysis: Roseman, Thombs.
Obtained funding: Thombs.
Administrative, technical, or material support: Thombs.
Study supervision: Thombs.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lexchin reports being a consultant to a law firm representing Apotex Inc in 2007, the Canadian federal government in a lawsuit challenging the Canadian ban on direct-to-consumer advertising of prescription drugs in 2007-2008, and a consultant to a law firm representing a plaintiff in a case against Allergan in 2010. The other authors report no disclosures for the past 3-year reporting period.
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Online-Only Materials: eAppendix and eTables 1-3 are available at http://www.jama.com.

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