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Reporting of financial conflicts of interest in meta-analyses of drug trials published in high-impact medical journals: comparison of results from 2017 to 2018 and 2009

Carla Benea¹, Kimberly A. Turner^{1,2}, Michelle Roseman³, Lisa A. Bero⁴, Joel Lexchin^{5,6}, Erick H. Turner^{7,8} and Brett D. Thombs^{1,2,9,10,11,12,13*}

Abstract

Background: A previous study found that 2 of 29 (6.9%) meta-analyses published in high-impact journals in 2009 reported included drug trials' funding sources, and none reported trial authors' financial conflicts of interest (FCOIs) or industry employment. It is not known if reporting has improved since 2009. Our objectives were to (1) investigate the extent to which pharmaceutical industry funding and author-industry FCOIs and employment from included drug trials are reported in meta-analyses published in high-impact journals and (2) compare current reporting with results from 2009.

Methods: We searched PubMed (January 2017–October 2018) for systematic reviews with meta-analyses including ≥ 2 randomized controlled trials (RCTs) of patented drugs. We included 3 meta-analyses published January 2017–October 2018 from each of 4 high-impact general medicine journals, high-impact journals from 5 specialty areas, and the Cochrane Database of Systematic Reviews, as in the previous study.

Results: Among 29 meta-analyses reviewed, 13 of 29 (44.8%) reported the funding source of included trials compared to 2 of 29 (6.9%) in 2009, a difference of 37.9% (95% confidence interval, 15.7 to 56.3%); this included 7 of 11 (63.6%) from general medicine journals, 3 of 15 (20.0%) from specialty medicine journals, and 3 of 3 (100%) Cochrane reviews. Only 2 of 29 meta-analyses (6.9%) reported trial author FCOIs, and none reported trial author-industry employment.

Protocol Publication: A protocol was uploaded to the Open Science Framework prior to initiating the study. <https://osf.io/8xt5p/>

Limitations: We examined only a relatively small number of meta-analyses from selected high-impact journals and compared results to a similarly small sample from an earlier time period.

Conclusions: Reporting of drug trial sponsorship and author FCOIs in meta-analyses published in high-impact journals has increased since 2009 but is still suboptimal. Standards on reporting of trial funding described in the forthcoming revised PRISMA statement should be adapted and enforced by journals to improve reporting.

Keywords: Financial conflicts of interest, Reporting, Meta-analysis, Research methods

* Correspondence: brett.thombs@mcgill.ca

¹Lady Davis Institute of the Jewish General Hospital, 4333 Cote Ste Catherine Road, Montreal, Quebec H3T 1E4, Canada

²Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Full list of author information is available at the end of the article



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Background

Financial conflicts of interest (FCOIs) in drug trials can influence trial design, drug dosages and comparators, data analysis, interpretation of findings, and the likelihood that favorable results are reported [1–7]. Industry-sponsored trials are approximately 30% more likely to report favorable efficacy results and conclusions than non-sponsored trials, and this is not explained by other trial elements associated with risk of bias [6]. Similarly, trials conducted by principal investigators with FCOIs have higher odds of reporting positive outcomes than trials led by non-affiliated principal investigators, controlling for trial funding source [7].

Meta-analyses are highly cited [8] and are prioritized in the development of clinical practice guidelines and in setting research priorities [9–11]. A review of a sample of 29 meta-analyses of drug trials published in high-impact medical journals in 2009, however, reported that only 2 (6.9%) reported funding sources and none reported author FCOIs or industry employment from included trials [12]. A 2012 review of 151 Cochrane reviews of drug trials found that only 46 (30.5%) reported the funding source of some or all included trials; only 16 (10.6%) provided any information on author FCOIs or industry employment [13].

In 2012, the Cochrane Collaboration began to require that funding sources and author FCOIs be reported for all trials included in Cochrane reviews [14–16]. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, which was published in 2009 [17, 18], however, did not address reporting of trial funding and author-industry financial ties from included trials. International Committee of Medical Journal Editors (ICMJE) guidelines require that meta-analysis authors declare their own FCOIs but do not address reporting of study funding or author FCOIs of included trials [19].

The objectives of this study were to (1) investigate the extent to which pharmaceutical industry funding and author-industry financial ties and employment from drug trials synthesized in meta-analyses are reported in meta-analyses published in high-impact journals and (2) compare current reporting with results from 2009 [12].

Methods

Our study protocol was published on the Open Science Framework (<https://osf.io/8xt5p/>) and followed the methods of the previous Roseman et al. [12] study with 2 exceptions. First, whereas the previous study was limited to a 10-month period (January to October 2009), we extended the period to 22 months a priori (January 2017 to October 2018) to improve the likelihood that we could include the same number of meta-analyses from each journal or specialty area. Second, in addition to extracting reporting of trial information in meta-analyses, the previous study [12] reviewed FCOIs from all included trials. Since it is well-established that FCOIs

are common in drug trials [1, 12, 20], we examined reporting in meta-analyses, but did not extract information from included trials.

Study selection

To be included, publications had to include at least 1 meta-analysis that (1) was part of a documented systematic review, (2) statistically combined results from ≥ 2 RCTs, (3) did not include non-RCTs, (4) evaluated the efficacy or harm of a drug or class of drugs, and (5) included at least 1 drug in any study arm under patent in the USA at the time of publication based on the electronic US Food and Drug Administration Orange Book [21]. Drugs were defined broadly to include biologics and vaccines but not nutritional supplements (e.g., vitamins) or medical devices without a drug component. Status of potential drug products not found in the FDA database, such as products registered as drugs only outside of the USA, was determined by review of team members and consensus. A drug was considered under patent if any aspect of the active ingredient (e.g., dosage, route, strength) was protected by an unexpired patent. We included the patent requirement to restrict the sample to drugs of potential economic importance to pharmaceutical companies. See Additional Methods 1 for the title/abstract and full-text eligibility coding guides.

Data sources and searches

We selected a sample of meta-analyses published from January 1, 2017, to October 25, 2018, in 3 categories of high-impact publications: (1) general medicine journals, (2) journals from 5 specialty medicine areas (oncology, cardiology, respiratory medicine, endocrinology, and gastroenterology), and (3) the Cochrane Database of Systematic Reviews [12].

In the previous study [12], among general medicine journals, we selected the 3 most recently published eligible meta-analyses from each journal with a 2008 impact factor ≥ 10 (*New England Journal of Medicine*, *JAMA*, *Lancet*, *BMJ*, *Annals of Internal Medicine*, *PLoS Medicine*) with fewer included if < 3 met eligibility criteria. Neither the *New England Journal of Medicine* nor *PLoS Medicine* had any eligible meta-analyses, and the *Annals of Internal Medicine* had only 2. Thus, in the present study, only meta-analyses from *JAMA*, *Lancet*, *BMJ*, and *Annals of Internal Medicine* were eligible, and we included only 2 meta-analyses from *Annals of Internal Medicine*.

In the previous study [12], we selected the top 5 specialty areas based on 2008 global pharmaceutical sales. For the present study, we included the same 5 specialty areas (oncology, cardiology, respiratory medicine, endocrinology, and gastroenterology). In each specialty area, we included the 3 most recently published eligible meta-analyses in the top impact factor journal in the specialty area based on the 2016 Clarivate Analytics Science Citation Index. If 3

eligible meta-analyses were not published in the top journal, we searched the journal with the next highest impact factor and continued in declining order of impact factor until 3 eligible meta-analyses were identified.

We searched MEDLINE via PubMed using limits of article type (“meta-analysis”) with journal names, supplemented by a manual search of each journal’s table of contents. Articles published online ahead of print, but not in the final format, as of the search date were not eligible. For articles published in the same journal issue, the one with the highest page number was considered most recent. In each Cochrane Database of Systematic Reviews issue, meta-analyses were reviewed in reverse sequence as the most recently published reviews are listed first.

Data extraction

We uploaded search results into the systematic review software DistillerSR® for inclusion and exclusion and result coding. Review of identified articles from each general medicine journal, specialty medicine area, and the Cochrane Database of Systematic Reviews was conducted independently by 2 reviewers, 1 article at a time, in reverse temporal sequence until the targeted number of eligible meta-analyses was obtained. Any disagreements were resolved by consensus, involving a third reviewer if necessary.

Two investigators independently reviewed all included meta-analyses, including disclosure statements, article texts and tables, author bylines and acknowledgments, and online journal supplements to identify (1) in the meta-analysis: disclosed funding sources, author-industry financial ties, author-industry employment, and whether a quality or risk of bias assessment was conducted, and (2) whether or not the meta-analysis reported trial funding, author-industry financial ties, and author-industry employment from included drug RCTs. See Additional Methods 2 for the Meta-Analysis Data Extraction dictionary. Additionally, in February 2020, we examined author instructions from all journals with included meta-analyses to determine if they included instructions on reporting of funding sources, author-industry financial ties, or author-industry employment for studies included in meta-analyses published in the journal.

Data synthesis and analysis

Study funding sources for meta-analyses were classified as pharmaceutical industry, non-industry (e.g., public granting agency, private not-for-profit granting agency), combined pharmaceutical industry and non-industry, no study funding, or not reported. Meta-analyses reported as funded “in part” by the pharmaceutical industry with no other indication of funding source or funded by a not-for-profit organization fully sponsored by pharmaceutical industry sources were coded as industry-funded. Industry funding was considered to be a provision of financial support, resources (e.g., statistical analyses), or study personnel.

Meta-analysis author financial ties to industry were defined per the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest [19] and included current or former board membership, current or former consultancy, former industry employment, equity holdings (e.g., stock ownership, stock options), expert testimony, gifts, patents (planned, pending, issued), payment for manuscript preparation, other research funding, royalties, speaker fees/ payment for presentation development, travel reimbursement, or other unspecified FCOIs, as disclosed in the article. If an article did not contain a disclosure statement, author-industry financial ties were coded as not reported. Authorship by persons employed by the pharmaceutical industry at the time of article publication was coded separately as “industry employment.”

For reporting in meta-analyses of trial funding, author-industry financial ties, and author-industry employment from included drug RCTs, for each category, we determined if the meta-analysis reported for all, some, or no included RCTs. When information was reported, we determined where information could be found in the meta-analysis (e.g., text, characteristics of studies table, risk of bias assessment, footnote).

Any discrepancies in data extraction were resolved by consensus, including consultation with a third reviewer if necessary.

We reported descriptive characteristics of included meta-analyses, their funding, and author-industry financial ties. To compare the proportion of meta-analyses that reported study funding, author financial ties, and author employment from included RCTs, we generated 95% confidence intervals (CIs) for the differences in proportions [22].

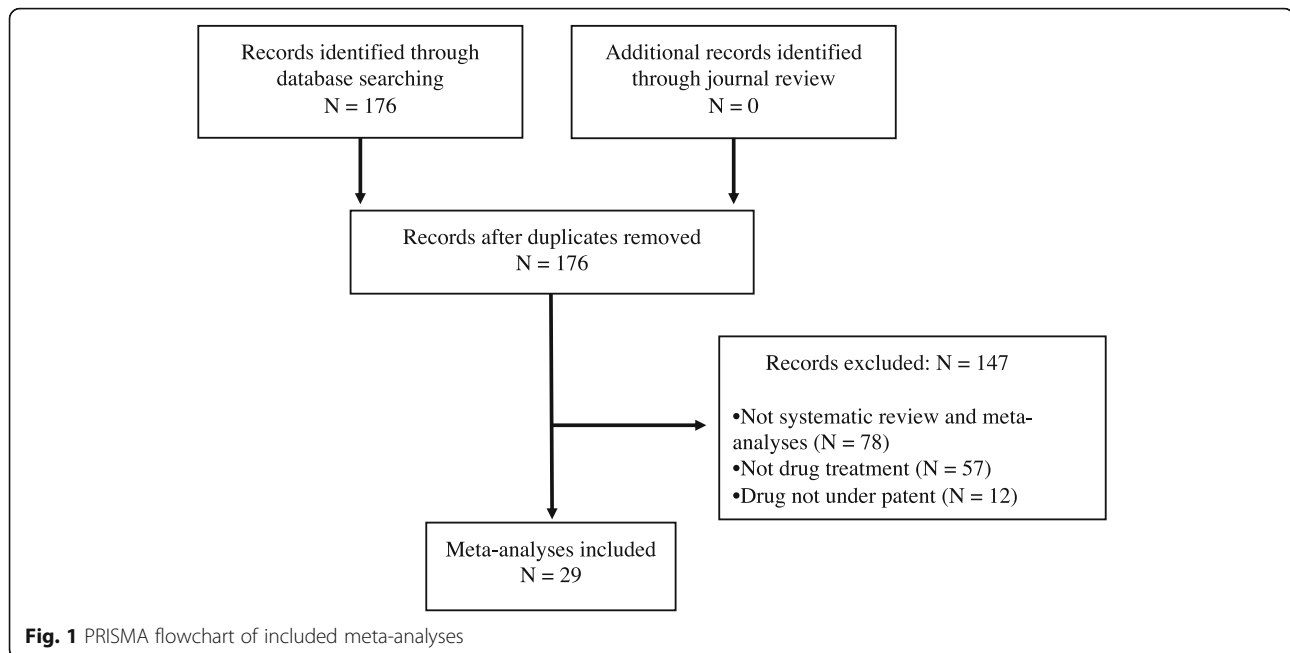
Role of the funding source

No funder had any role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. Dr. Thombs had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Article selection

A total of 176 publications were reviewed (37 from general medicine journals, 121 from specialty medicine journals, 18 from the Cochrane Database of Systematic Reviews) to obtain the 29 that were included in the review (Fig. 1) [23–51]. As shown in Table 1, impact factors of journals with included publications ranged from 17.2 to 47.8 in general medicine, 11.9 to 24.0 in oncology, 19.3 to 19.9 in cardiology, 10.3 to 10.6 in respiratory medicine, 11.9 to 19.7 in endocrinology, 16.7 to 18.4 in gastroenterology, and 6.3 for the Cochrane Database of Systematic Reviews. The 29 selected meta-analyses evaluated a broad spectrum of pharmacological interventions, including 11 on treatment efficacy [24, 29, 33, 35, 36, 40, 42, 44–47], 2 on harms [31, 50], and 16



[23, 25, 28, 30, 32, 34, 37–39, 41, 43, 48, 49, 51] on both efficacy and harms. Between 2 and 522 RCTs were included in each meta-analysis. None of the journals with included meta-analyses mentioned reporting of funding or author FCOI of studies included in meta-analyses that are published in the journal.

Study funding and author-industry financial ties of meta-analyses

As shown in Tables 1 and 2 of 29 (6.9%) included meta-analyses, both published in specialty journals [34, 43], reported receiving pharmaceutical industry funding, 11 (37.9%) reported non-industry funding [23, 26, 29–32, 35, 40, 49–51], 3 reported no study funding (10.3%) [28, 33, 46], and the funding source of 13 (44.8%) was not reported [24, 25, 27, 36–39, 41, 42, 44, 45, 47, 48]. Meta-analysis funding sources were reported for 8 of 11 meta-analyses from general medicine journals (72.7%) [23, 26, 28–33], 5 of 15 (33.3%) from specialty medicine journals [34, 35, 40, 43, 46], and all 3 (100%) Cochrane reviews [49–51].

All 29 meta-analyses included author COI statements. In 15 of the 29 meta-analyses (51.7%), at least 1 author reported 1 or more financial ties to the pharmaceutical industry [24–26, 29, 34, 35, 37–40, 43, 45, 47, 49, 50], whereas all authors reported no financial ties in 14 (48.3%) [23, 27, 28, 30–33, 36, 41, 42, 44, 46, 48, 51]. In 5 of 29 (17.2%) meta-analyses [34, 35, 38, 39, 43], all published in specialty medicine journals and including the 2 meta-analyses with industry funding [34, 43], the majority of authors had financial ties to industry. Author-industry financial ties were present in 4 of 11 meta-analyses published in general medicine journals

(36.4%) [24–26, 29], 9 of 15 (60.0%) in specialty medicine journals [34, 35, 37–40, 43, 45, 47], and 2 of 3 (66.7%) Cochrane reviews [49, 50]. Specific types of author ties to industry are shown in Table 2.

Reporting of trial funders and author FCOI from RCTs included in meta-analyses

As shown in Table 3, 13 of 29 (44.8%) meta-analyses reported the funding sources of included RCTs; 12 reported for all included RCTs [23, 24, 26, 27, 29, 30, 32, 34, 45, 49–51], whereas 1 reported for 5 of 7 included RCTs [39]. Funding sources of included RCTs were reported for 7 of 11 (63.6%) meta-analyses from general medicine journals [23, 24, 26, 27, 29, 30, 32], 3 of 15 (20.0%) from specialty medicine journals [34, 39, 45], and for all 3 (100%) Cochrane reviews [49–51]. The mean, median, and range of the number of RCTs in meta-analyses that reported trial funding sources were 52.9, 13, and from 2 to 522, respectively. For those that did not report funding sources, they were 29.2, 16, and from 3 to 236, respectively.

Only 2 of the 29 meta-analyses (6.9%) reported trial author-industry financial ties, including 1 from a general medicine journal [24] and 1 Cochrane review [49]. None of the 29 meta-analyses reported industry employment status of included RCT authors. See Fig. 2.

Comparison of reporting of industry funding of included RCTs in 2017–2018 versus 2009

The overall percentage of meta-analyses of drug treatments that reported the funding source of included RCTs increased from 6.9% (2 of 29) in 2009 to 44.8% (13 of 29) in 2017–2018, a difference of 37.9% (95% CI,

Table 1 Characteristics of included meta-analyses

| Author | Journal/year | 2016 impact factor | Number of drug RCTs in meta-analysis | Publication dates of articles reviewed | Setting/diagnosis | Pharmacological intervention | Comparison arm(s) | Efficacy/harm | Funding source | Number of authors with disclosed industry financial ties/number of authors | Number of authors employed by industry/number of authors |
|---------------------------|---------------------|--------------------|--------------------------------------|--|--|--|--|-------------------|------------------|--|--|
| General medicine | | | | | | | | | | | |
| Feller et al. [23] | JAMA/2018 | 44.4 | 21 | 1984–2017 | Non-pregnant adults with subclinical hypothyroidism | Thyroid hormone therapy | Placebo, no intervention | Efficacy and harm | Non-industry | 0/15 | 0/15 |
| McIntyre et al. [24] | JAMA/2018 | 44.4 | 23 | 1999–2017 | Patients with distributive shock | Vasopressin—4 included plus catecholamine vasopressors | Catecholamines vasopressors—2 included | Efficacy | Not reported | 2/10 | 0/10 |
| Zheng et al. [25] | JAMA/2018 | 44.4 | 236 | 2004–2017 | Patients with type 2 diabetes | NMA: SGLT-2 inhibitors, GLP-1 agonists, DPP-4 inhibitors | Placebo, no treatment | Efficacy and harm | Not reported | 1/7 | 0/7 |
| Cipriani et al. [26] | Lancet/2018 | 47.8 | 522 | 1979–unpublished | Adults with major depressive disorder | NMA: antidepressants—21 included | Placebo | Efficacy and harm | Non-industry | 4/18 | 0/18 |
| Gayet-Ageron et al. [27] | Lancet/2018 | 47.8 | 2 | 2010–2017 | Patients with acute severe hemorrhage | Tranexamic acid | Placebo | Efficacy and harm | Not reported | 0/6 | 0/6 |
| Jinathongthai et al. [28] | Lancet/2017 | 47.8 | 40 | 1986–2005 | Patients with ST-segment elevation myocardial infarction | NMA: fibrinolytic agents—4 included, parenteral anticoagulants—4 included, Gp IIb/IIIa inhibitors—3 included, antiplatelets—3 included | N/A | Efficacy and harm | No study funding | 0/8 | 0/8 |
| Alibhai et al. [29] | Ann Intern Med/2017 | 17.2 | 23 ^a | 2001–2014 | Men with non-metastatic prostate cancer | Bisphosphonates—5 included | Placebo | Efficacy | Non-industry | 3/9 | 0/9 |
| Wilson et al. [30] | Ann Intern Med/2017 | 17.2 | 10 ^b | 2003–2012 | Adults with chronic kidney disease | Bisphosphonates—4 included, raloxifene, denosumab, teriparatide | Placebo, no treatment, active control | Efficacy and harm | Non-industry | 0/8 | 0/8 |
| Baxi et al. [31] | BMJ/2018 | 20.8 | 13 | 2015–2017 | Patients with cancer with recurrent or metastatic disease | AntiPD-1—3 included | Chemotherapy drug, small molecule inhibitor, investigators' choice | Harm | Non-industry | 0/7 | 0/7 |
| López-López et al. [32] | BMJ/2017 | 20.8 | 23 | 1989–2014 | Adults with non-valvular atrial fibrillation eligible for oral anticoagulation | DOACs—5 included | Warfarin or other vitamin K antagonist, aspirin, clopidogrel | Efficacy and harm | Non-industry | 0/18 | 0/18 |

Table 1 Characteristics of included meta-analyses (Continued)

| Author | Journal/year | 2016 impact factor | Number of drug RCTs in meta-analysis | Publication dates of articles reviewed | Setting/diagnosis | Pharmacological intervention | Comparison arm(s) | Efficacy/harm | Funding source | Number of authors with disclosed industry financial ties/number of authors | Number of authors employed by industry/number of authors |
|------------------------------|---------------------------------|--------------------|--------------------------------------|--|---|---|-------------------------|-------------------|--|--|--|
| Sadeghirad et al. [33] | BMJ/2017 | 208 | 10 | 1993–2017 ^c | Patients with sore throat | Corticosteroids—3 included | Placebo, standard care | Efficacy | No study funding | 0/9 | 0/9 |
| Specialty journals | | | | | | | | | | | |
| Oncology | | | | | | | | | | | |
| McCarthy et al. [34] | J Clin Oncol/2017 | 24.0 | 3 | 2012–2014 | Patients with newly diagnosed multiple myeloma | Lenalidomide | Placebo or observation | Efficacy and harm | Industry financial support and resource ^d | 15/19 | 4/19 |
| van Beurden-Tian et al. [35] | J Clin Oncol/2017 | 24.0 | 17 | 2005–2016 | Adults with relapsed and/or refractory multiple myeloma | NMA: 18 treatments for multiple myeloma | N/A | Efficacy | Non-industry | 5/5 | 0/5 |
| Abdel-Qadir et al. [36] | Ann Oncol/2017 | 11.9 | 16 | 1983–2013 | Adults with cancer | NMA: dexrazoxane, angiotensin antagonist, beta-blockers, statins, co-enzyme Q-10, prenylamine, N-acetylcysteine | Placebo or no treatment | Efficacy | Not reported | 0/7 | 0/7 |
| Cardiology | | | | | | | | | | | |
| Siontis et al. [37] | Circulation/2017 | 19.3 | 4 | 2014–2016 | Patients with valvular heart disease | DOAC—4 included | Warfarin | Efficacy and harm | Not reported | 1/4 | 0/4 |
| Renda et al. [38] | J Am Coll Cardiol/2017 | 19.9 | 4 | 2009–2013 | Patients with atrial fibrillation and valvular heart disease | NOAC—4 included | Warfarin | Efficacy and harm | Not reported | 3/4 | 0/4 |
| Lau et al. [39] | J Am Coll Cardiol/2017 | 19.9 | 7 | 2007–2015 | Patients with coronary artery disease | Potent P2Y12 inhibitors—3 types included | Placebo or clopidogrel | Efficacy and harm | Not reported | 13/16 | 0/16 |
| Respiratory medicine | | | | | | | | | | | |
| Verberkt et al. [40] | Eur Respir J/2017 | 10.6 | 22 ^e | 1982–2015 | Patients with chronic breathlessness due to advanced disease | Opioids—8 included | Placebo | Efficacy | Non-industry | 3/9 | 0/9 |
| Ding et al. [41] | J Thorac Oncol/2017 | 10.3 | 16 | 2008–2015 | Treatment-naïve patients with advanced EGFR-mutant non-small cell lung cancer | EGFR TKI—3 included | EGFR TKI—3 included | Efficacy and harm | Not reported | 0/8 | 0/8 |
| Lee et al. [42] | J Thorac Oncol/2017 | 10.3 | 3 | 2015–2016 | Patients with metastatic EGFR-mutated non-small cell lung cancer | Immune checkpoint inhibitors—3 included | Docetaxel | Efficacy | Not reported | 0/7 | 0/7 |
| Endocrinology | | | | | | | | | | | |
| Bethel et al. [43] | Lancet Diabetes Endocrinol/2018 | 19.7 | 4 | 2015–2017 | Adults with type 2 diabetes | GLP-1 receptor agonists—4 included | Placebo | Efficacy and harm | Industry financial support | 15/17 | 3/17 |

Table 1 Characteristics of included meta-analyses (Continued)

| Author | Journal/year | 2016 impact factor | Number of drug RCTs in meta-analysis | Publication dates of articles reviewed | Setting/diagnosis | Pharmacological intervention | Comparison arm(s) | Efficacy/harm | Funding source | Number of authors with disclosed industry financial ties/number of authors | Number of authors employed by industry/number of authors | |
|-------------------------|---------------------------------|--------------------|--------------------------------------|--|---|---|--|-------------------|------------------|--|--|--|
| de Carvalho et al. [44] | Diabetes Care/2018 | 11.9 | 20 | 2012–2016 | Participants with familial or non-familial hypercholesterolemia | PCSK9 inhibitors—3 included | Placebo, ezetimibe, atorvastatin, rosuvastatin, standard therapy | Efficacy | Not reported | 0/3 | 0/3 | |
| Maiorino et al. [45] | Diabetes Care/2017 | 11.9 | 26 | 2011–2016 | Adults with type 2 diabetes | Insulin regimens plus GLP-1 receptor agonists | Insulin regimens | Efficacy | Not reported | 2/6 | 0/6 | |
| Gastroenterology | | | | | | | | | | | | |
| Khera et al. [46] | Gastroenterology/2018 | 18.4 | 28 | 1998–2015 | Obese or overweight adults | NMA: orlistat, lorcaserin, naltrexone-bupropion, liraglutide, phentermine-topiramate | Alternate treatment or placebo | Efficacy | No study funding | 0/9 | 0/9 | |
| Nelson et al. [47] | GUT/2017 | 16.7 | 21 | 2003–2015 | Adults with chronic idiopathic constipation | NMA: diphenyl methanes or derivatives—2 included, 5-HT4 receptor agonists—3 included, GC-C receptor agonist—1 included, chloride channel type 2 opener—1 included, apical sodium bile acid—1 included | N/A | Efficacy | Not reported | 1/9 | 0/9 | |
| Ford et al. [48] | GUT/2017 | 16.7 | 13 | 1986–2015 | Adults (participants aged > 16 years) with functional dyspepsia | Psychotropic drugs—6 classes | Placebo | Efficacy and harm | Not reported | 0/6 | 0/6 | |
| Cochrane reviews | | | | | | | | | | | | |
| Tenforde et al. [49] | Cochrane Database Syst Rev/2018 | 6.3 | 13 | 1997–2018 | Adults with HIV-associated cryptococcal meningitis | NMA: antifungal drugs, adjunctive drugs | N/A | Efficacy and harm | Non-industry | 1/7 | 0/7 | |
| McNicol et al. [50] | Cochrane Database Syst Rev/2018 | 6.3 | 11 ^f | 1992–2012 | Pediatric patients with postoperative pain | Ketorolac | Placebo, opioid | Harm | Non-industry | 1/3 | 0/3 | |
| Normansell et al. [51] | Cochrane Database Syst Rev/2018 | 6.3 | 4 ^g | 1974–2016 | Adults and children with exacerbations of asthma | Macrolide antibiotics—3 included, penicillin—2 included | Placebo | Efficacy and harm | Non-industry | 0/6 | 0/6 | |

5-HT4 5-hydroxytryptamine receptor 4, **DOAC** direct-acting oral anticoagulant, **DPP-4** dipeptidyl peptidase 4, **EGFR** epidermal growth factor receptor, **GC-C** guanylate cyclase C, **GLP-1** glucagon-like peptide-1, **Gp IIb/IIIa** glycoprotein IIb/IIIa, **N/A** not applicable (no placebo or no treatment arm in NMA), **NMA** network meta-analysis, **NOAC** non-vitamin K antagonist oral anticoagulants, **PCSK9** proprotein convertase subtilisin/kexin type 9, **PD-1** programmed cell death protein 1, **SGLT-2** sodium-glucose cotransporter 2, **TKI** tyrosine kinase inhibitors

^aThe systematic review included 27 RCTs in total, of which 23 had their results pooled

^bThe systematic review included 13 RCTs in total, of which 10 had their results pooled

^cThe date for 1 of the included RCTs was reported as 1994 in a single figure and 1993 in all other instances; therefore, 1993 was used as the beginning of the date range of included studies

^dThe systematic review included an acknowledgment thanking Kristina Hernandez and Peter Simon for medical writing assistance, sponsored by Celgene Corporation, which was coded as industry funding in the form of resources

^eThe systematic review included 35 RCTs in total, of which 22 had their results pooled

^fThe systematic review included 13 RCTs in total, of which 11 had their results pooled

^gThe systematic review included 6 RCTs in total, of which 4 had their results pooled

Table 2 Financial ties to the pharmaceutical industry among authors of reviewed meta-analyses (Continued)

| Author | Journal | Number of authors | Authors that reported any industry financial ties | Authors that reported industry board membership | Authors that reported industry consultancy | Authors that reported equity holdings | Authors that reported research funding from industry | Authors that reported holding patents | Authors that reported receiving royalties | Authors that reported payment for development of presentations | Authors that reported receiving travel reimbursement | Authors that reported receiving unspecified FCOI |
|-------------------------|----------------------------|-------------------|---|---|--|---------------------------------------|--|---------------------------------------|---|--|--|--|
| Lee et al. [42] | J Thorac Oncol | 7 | 0/7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Endocrinology | | | | | | | | | | | | |
| Bethel et al. [43] | Lancet Diabetes Endocrinol | 17 | 15/17 | 5 ^d | 2 | 2 | 8 | 0 | 0 | 2 | 1 | 7 ^e |
| de Carvalho et al. [44] | Diabetes Care | 3 | 0/3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Maiorino et al. [45] | Diabetes Care | 6 | 2/6 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Gastroenterology | | | | | | | | | | | | |
| Khera et al. [46] | Gastroenterology | 9 | 0/9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nelson et al. [47] | GUT | 9 | 1/9 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Ford et al. [48] | GUT | 6 | 0/6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total—specialty: | | | 9/15 | | | | | | | | | |
| Cochrane reviews | | | | | | | | | | | | |
| Tenforde et al. [49] | Cochrane Database Syst Rev | 7 | 1/7 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| McNicol et al. [50] | Cochrane Database Syst Rev | 3 | 1/3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Normansell et al. [51] | Cochrane Database Syst Rev | 6 | 0/6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total Cochrane | | | 2/3 | | | | | | | | | |

^aOne author reported receiving “personal fees” from industry but did not specify further, and this was coded as unspecified FCOI

^bOne author reported “consulting fees, honoraria, or both” which was coded as unspecified FCOI

^cOnly 5 authors out of 9 provided ICME forms for disclosure of potential FCOIs in the supplemental material; the information was not reported elsewhere

^dBeing a member of the board for the non-profit organization “AstraZeneca HealthCare Foundation” was considered as industry board membership

^eFour authors reported receiving “personal fees” but did not specify further, 1 author reported receiving “grants or honoraria for consultancy or lectures,” 1 reported “honorarium for steering committee attendance,” 1 reported honoraria for “participation in study committees,” and 1 reported honoraria for “participation in academic conferences”; these were all coded as unspecified FCOIs

Table 3 Disclosure and reporting in meta-analyses of randomized controlled trial funding source, author financial ties to the pharmaceutical industry, and author employment by the pharmaceutical industry

| Author | Journal | Number of meta-analyzed RCTs | Meta-analysis reported RCT funding | Place in publication of RCT funding | Meta-analysis reported RCT author-industry financial ties | Place in publication of RCT author-industry financial ties | Meta-analysis reported RCT author-industry employment | Quality or risk assessment method of meta-analysis |
|-------------------------------|----------------|------------------------------|---|---|---|--|---|--|
| General medicine | | | | | | | | |
| Feller et al. [23] | JAMA | 21 | Yes, for each included study | Text (as summary statement—for some but not all included studies—RCTs referenced) Characteristics of included studies table (in article—for each included study) | No | N/A | No | Cochrane |
| McIntyre et al. [24] | JAMA | 23 | Yes, for each included study | Characteristics of included studies table (in supplementary material—web link only—no mention in text) | Yes, for some but not all included studies ^a | Characteristics of included studies table (in supplementary material—web link only—no mention in text) | No | Cochrane |
| Zheng et al. [25] | JAMA | 236 | No | N/A | No | N/A | No | Cochrane |
| Cipriani et al. [26] | Lancet | 522 | Yes, for each included study ^a | Text (as summary statement—RCTs not referenced) Characteristics of included studies (in supplementary material—web link only—funder name not mentioned) Abstract | No ^c | N/A | No | Cochrane |
| Gayet-Ageron et al. [27] | Lancet | 2 | Yes, for each included study | Abstract | No | N/A | No | Cochrane |
| Jinathongthai et al. [28] | Lancet | 40 | No | N/A | No | N/A | No | Cochrane |
| Alibhai et al. [29] | Ann Intern Med | 23 | Yes, for each included study | Risk of bias assessment text section (as summary statement—for some but not all included studies—RCTs not referenced) Risk of bias assessment table (in article—for each included study) | No | N/A | No | Cochrane |
| Wilson et al. [30] | Ann Intern Med | 10 | Yes, for each included study ^d | Risk of bias assessment text section (as summary statement—RCTs referenced) Characteristics of studies included table (in article—for each included study) | No | N/A | No | Cochrane |
| Baxi et al. [31] | BMJ | 13 | No | N/A | No | N/A | No | Cochrane |
| López-López et al. [32] | BMJ | 23 | Yes, for each included study | Text (as summary statement—RCTs not referenced) Characteristics of included studies table (for each included study—in supplementary material—web link only) | No | N/A | No | Cochrane |
| Sadeghirad et al. [33] | BMJ | 10 | No | N/A | No | N/A | No | Cochrane |
| General medicine total | | 923 | 7/11 (63.6%) | | 1/11 (9.1%) | | 0/11 (0.0%) | |

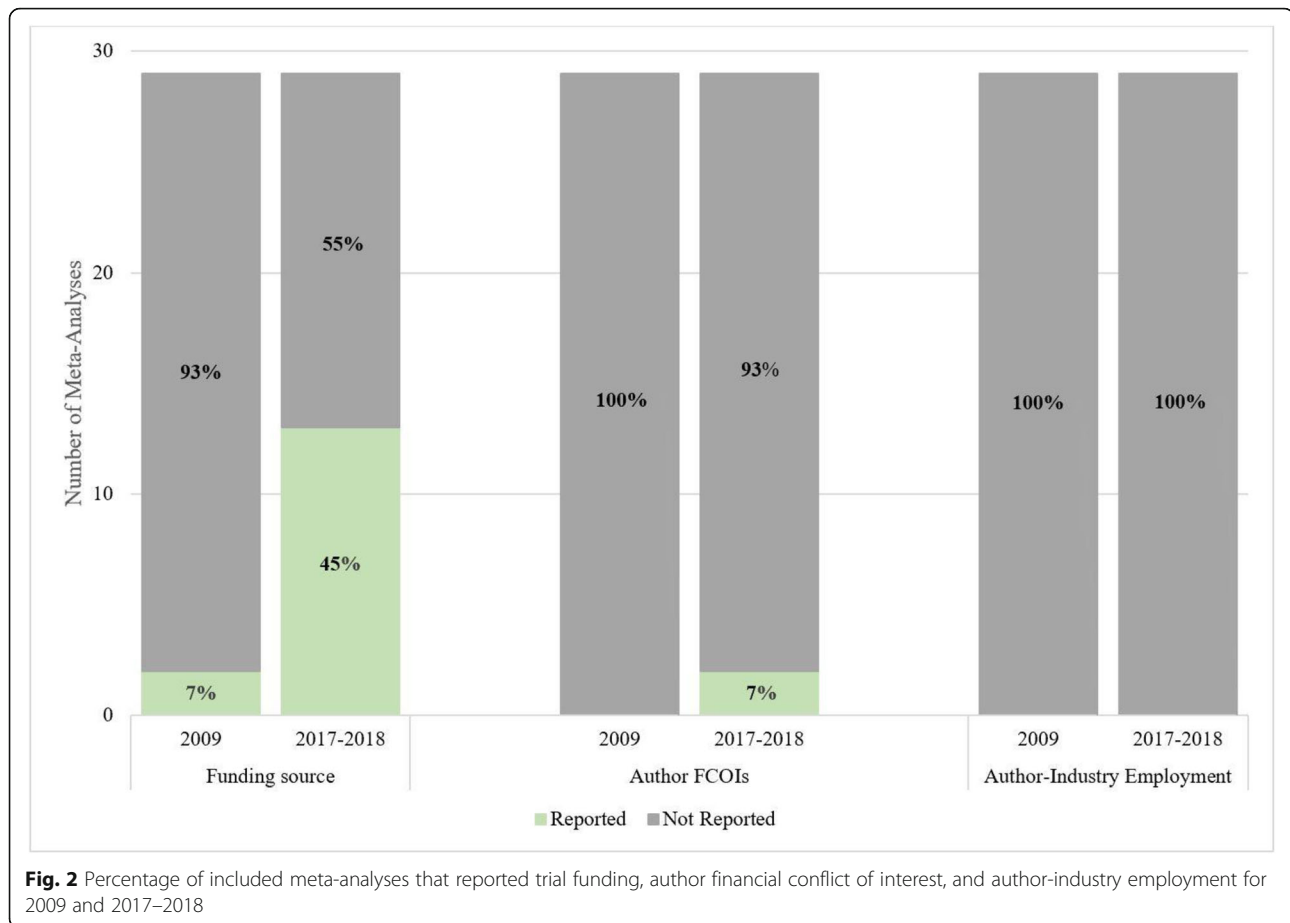
Table 3 Disclosure and reporting in meta-analyses of randomized controlled trial funding source, author financial ties to the pharmaceutical industry, and author employment by the pharmaceutical industry (*Continued*)

| Author | Journal | Number of meta-analyzed RCTs | Meta-analysis of reported RCT funding | Place in publication of RCT funding | Meta-analysis reported RCT author-industry financial ties | Place in publication of RCT author-industry financial ties | Meta-analysis reported RCT author-industry employment | Quality or risk assessment method of meta-analysis |
|-----------------------------|----------------------------|------------------------------|--|---|---|--|---|--|
| Specialty medicine | | | | | | | | |
| Oncology | | | | | | | | |
| McCarthy et al. [34] | J Clin Oncol | 3 | Yes, for each included study | "Support" section at end of article | No | N/A | No | None |
| van Beurden-Tan et al. [35] | J Clin Oncol | 17 | No | N/A | No | N/A | No | None |
| Abdel-Qadir et al. [36] | Ann Oncol | 16 | No | N/A | No | N/A | No | Cochrane |
| Cardiology | | | | | | | | |
| Siontis et al. [37] | Circulation | 4 | No | N/A | No | N/A | No | None |
| Renda et al. [38] | J Am Coll Cardiol | 4 | No | N/A | No | N/A | No | Cochrane |
| Lau et al. [39] | J Am Coll Cardiol | 7 | Yes, for some but not all studies ^e | Footnote on first 3 pages of article | No | N/A | No | None |
| Respiratory medicine | | | | | | | | |
| Verberkt et al. [40] | Eur Resp J | 22 | No | N/A | No | N/A | No | Cochrane |
| Ding et al. [41] | J Thorac Oncol | 16 | No | N/A | No | N/A | No | None |
| Lee et al. [42] | J Thorac Oncol | 3 | No | N/A | No | N/A | No | None |
| Endocrinology | | | | | | | | |
| Bethel et al. [43] | Lancet Diabetes Endocrinol | 4 | No | N/A | No | N/A | No | Jadad |
| de Carvalho et al. [44] | Diabetes Care | 20 | No | N/A | No | N/A | No | Cochrane |
| Maiorino et al. [45] | Diabetes Care | 26 | Yes, for each included study | Text (as summary statement—RCTs not referenced) Characteristics of included studies table (in article—for each included study) | No | N/A | No | Cochrane, Jadad |
| Gastroenterology | | | | | | | | |
| Khera et al. [46] | Gastroenterology | 28 | No | N/A | No | N/A | No | Cochrane |

Table 3 Disclosure and reporting in meta-analyses of randomized controlled trial funding source, author financial ties to the pharmaceutical industry, and author employment by the pharmaceutical industry (Continued)

| Author | Journal | Number of meta-analyzed RCTs | Meta-analysis reported RCT funding | Place in publication of RCT funding | Meta-analysis reported RCT author-industry financial ties | Place in publication of RCT author-industry financial ties | Meta-analysis reported RCT author-industry employment | Quality or risk assessment method of meta-analysis |
|--|----------------------------|------------------------------|------------------------------------|--|---|---|---|--|
| Nelson et al. [47] | Gut | 21 | No | N/A | No | N/A | No | Cochrane |
| Ford et al. [48] | Gut | 13 | No | N/A | No | N/A | No | Cochrane |
| Specialty medicine total: | | 204 | 3/15 (20.0%) | | 0/15 (0.0%) | | 0/15 (0.0%) | |
| Cochrane database of systematic reviews | | | | | | | | |
| Tenforde et al. [49] | Cochrane Database Syst Rev | 13 | Yes, for each included study | Risk of bias assessment in main text (as a summary statement—for some but not all included studies—RCTs referenced) ¹ Risk of bias assessment table in characteristics of included studies section (supplementary material—in article—for some but not all included studies) ⁹ Characteristics of included studies table (supplementary material—in article—for each included study) | Yes, for each included study | Risk of bias assessment in main text (as a summary statement—for some but not all included studies—studies referenced) ¹ Risk of bias assessment table in characteristics of included studies section (supplementary material—in article—for some but not all included studies) ⁹ Characteristics of included studies table (supplementary material—in article—for each included study) | No | Cochrane |
| McNicol et al. [50] | Cochrane Database Syst Rev | 11 | Yes, for each included study | Characteristics of included studies table (supplementary material—in article) | No | N/A | No | Cochrane |
| Normansell et al. [51] | Cochrane Database Syst Rev | 4 | Yes, for each included study | Text (as a summary statement—RCTs referenced) Characteristics of included studies table (supplementary material—in article—for each included study) | No ¹ | N/A | No | Cochrane |
| Cochrane total | | 28 | 3/3 (100%) | | 1/3 (33.3%) | | 0/3 (0.0%) | |
| Total | | 1155 | 13/29 (44.8%) | | 2/29 (6.9%) | | 0/29 (0.0%) | |

FCOI financial conflict of interest, N/A not applicable, RCT randomized controlled trial
^aAuthor FCOIs are reported for 21 out of 23 RCTs. Reporting of “All authors submitted the ICJME Form for Disclosure” for 1 study was not considered reporting of author FCOIs. Reporting of “Funding source: Ferring pharmaceuticals, patents related to the use of vasopressin in septic shock” for 1 study was not considered reporting of author FCOIs since not specified and was only coded as RCT funding source reported
^bThe authors considered funding for included studies as “sponsored” when it was indicated anywhere in the text that the study was funded/sponsored by the company which manufactured or marketed the drug in question, or if 1 or more of the authors were affiliated with the company in question, or if the data came from the documents provided by or obtained from the company website. Sponsorship was rated as “unclear” if the authors only listed the names of the companies in question in their declaration of conflicts of interest. Names of the pharmaceutical companies that sponsored trials were not reported
^cAuthor FCOIs with manufacturer of researched drug, among funding from manufacturer, or data obtained from manufacturer, qualified a study of “sponsored,” but no further specification was given. A study being “sponsored” was only coded as having funding sources reported
^dAuthors reported RCT funding of industry, not industry, or not reported, and sponsors’ names were not mentioned
^eFunding was reported for 5 out of 7 included RCTs
^fIn risk of bias assessment text section, the summarized “other bias” optional Cochrane domain included both direct support from pharmaceutical manufacturers of study drugs and authors receiving research support from manufacturers without the role of the drug companies clearly stated. Studies are referenced, but it is not mentioned for which FCOI (direct support from industry and/or author support from industry)
^gIn the “other bias” optional Cochrane domain in risk of bias assessment table, located in the characteristics of included studies section, funding is only reported for RCTs sponsored by pharmaceutical industry, with no mention of the name of the pharmaceutical company, which is only mentioned in the “Notes” section of the characteristics of included studies table
^hIn “other bias” optional Cochrane domain in risk of bias assessment table, located in the characteristics of included studies section, author FCOIs are only reported for RCTs where FCOIs are listed
ⁱAuthors stated that they extracted data on “notable conflicts of interest of trial authors” but no information on included RCTs author FCOIs was reported in the text or supplementary materials



15.7 to 56.3%). This included an increase from 0% (0 of 11) to 63.6% (7 of 11) in general medicine journals (difference 63.6%; 95% CI, 25.3 to 84.8%), an increase from 6.7% (1 of 15) to 20.0% (3 of 15) in specialty medicine journals (difference 13.3%; 95% CI, - 13.2 to 39.1%), and an increase from 1 of 3 (33.3%) to 3 of 3 (100%) among Cochrane reviews.

Discussion

The main finding was that the reporting of funding sources of drug trials included in meta-analyses in high-impact journals improved, from 2 of 29 (6.9%) in 2009 to 13 of 29 (44.8%) in 2017–2018, but it continues to be sub-optimal. Only 2 of 29 (6.9%) meta-analyses provided information on author-industry financial ties from included trials, and no meta-analyses reported if industry employees were involved in the trials.

In 2012, the Cochrane Collaboration began to require that trial funding sources and conflicts of interest of authors of included trials be reported in the “characteristics of included studies” table of all Cochrane reviews [15], and this is still mandatory [16]. We evaluated 3 Cochrane reviews, and all 3 reported trial funding sources, but only 1 of 3 provided information on author-

industry financial ties from included trials. A recent study [52] that investigated the extent to which recently published meta-analyses reported trial funding, author-industry financial ties, and author-industry employment from included RCTs found that reporting of trial funding in Cochrane meta-analyses increased from 30% (46 of 151 reviews) in 2010 to 84% (90 of 107) in 2016–2018. Reporting of trial author-industry financial ties increased from 7% (11 of 151) in 2010 to 44% (47 of 107) in 2016–2018, which suggests that this could still improve. Non-Cochrane meta-analyses published in 2016–2018 reported funding sources of included studies 15% of the time (21 of 143) and author-industry financial ties from included trials 1% of the time (2 of 143).

Cochrane reviews are recognized for their rigor [53] and often seen as the standard for systematic reviews on the benefits and harms of health care interventions [54, 55]. Consistent with this, Cochrane reporting standards are highlighted on the PRISMA website [56]. Ideally, the Cochrane Collaboration would ensure that authors of reviews adhere to both the requirement to report funding of trials included in reviews and to report author-industry financial ties from those trials. Nonetheless, Cochrane provides an example of how institutional

commitment can lead to change on a large scale, which suggests that other journals could achieve similar results, but that it would require explicit guidance from journal editors and enforcement of that guidance.

The original PRISMA statement, which was published in 2009, did not address reporting of the funding sources of studies included in systematic reviews and meta-analyses or the FCOIs of study authors [17, 18]. An updated PRISMA statement is forthcoming and, though not completed, based on a preliminary version will likely encourage, though not required, reporting of funding and author FCOI from studies included in systematic reviews and meta-analyses (personal communication, David Moher, February 13, 2020). It is possible that including encouragement to report on funding and FCOI in PRISMA could improve reporting, but the lack of a strong requirement and inclusion as an item in the checklist itself and the general low adherence to PRISMA [57] suggests that this may not have a strong effect.

It is not clear why general medicine journals improved in reporting between 2009 and the present study. It is unlikely related to PRISMA, since the existing PRISMA statement does not touch upon this issue. It is possible that this may be due to a more general awareness of these issues, that Cochrane added this requirement for its reviews, or a higher scrutiny by editors of these journals than previously or compared to specialty journals. None of the general medicine or specialty journals included in our review mention the reporting of funding sources or author FCOI from studies included in systematic reviews in their instructions to authors. Ideally, the forthcoming PRISMA checklist would include funding and FCOI of studies included in systematic reviews and meta-analyses as a dedicated item, which could support improvements in reporting, if adopted and enforced by reviewers and editors.

We previously recommended that the Cochrane Risk of Bias tool [58] be revised to include risk of bias due to industry sponsorship of trials and FCOIs of trial investigators [12]. This would be consistent with empirical evidence that has linked both sponsorship and other FCOIs to trial outcomes, controlling for other factors known to be associated with bias [6, 7, 14]. There is no, however, consensus on this approach [14, 59]. Currently, an alternative is being created to explicitly address risk of bias from industry sponsorship of trials and author-industry financial ties in Cochrane reviews, the Tool for Addressing Conflicts of Interest in Trials (TACIT) [60]. Once completed, TACIT will include a Conflicts of Interest Grid, which will facilitate a systematic collection of relevant information and allow for determination of when there is notable concern, which may then be integrated into an assessment of risk of bias. In the present study, only 3 meta-analyses, 1 of which was a Cochrane review,

attempted to incorporate funding sources of included trials into an assessment of risk of bias.

In interpreting results from this study, there are limitations to consider. First, the focus of the study was on reporting of trial funding and trial author FCOIs, and it was not designed to assess whether these were associated with meta-analysis quality or with the results of meta-analyses. Second, in replicating the methods of the previous study from 2009 [12], we selected 29 meta-analyses from high-impact journals in general medicine and 5 specialty areas for review; thus, it is not known to what degree these results may be generalizable to other areas of medicine or to lower impact journals. Third, we examined only a relatively small number of meta-analyses and compared results to a similarly small sample from an earlier time period.

Conclusion

In summary, reporting of funding sources of included trials in meta-analyses of drug treatments published in high-impact journals has improved since 2009 but is still alarmingly low. Fewer than half of the meta-analyses we reviewed reported funding sources of included trials, and fewer than a third provided information on trial funding in the main meta-analysis report. Reporting of trial author FCOIs and industry employment is even more concerning. Only 2 studies reported trial author-industry financial ties, and none directly reported whether industry employees were authors of included trials. Confidence in medical research and the quality of care delivered by those who rely on evidence from meta-analyses depends on transparent reporting and the ability to evaluate the degree to which conflicts of interest may have influenced trial design, conduct, and outcomes. The forthcoming revised PRISMA statement will require transparent reporting of funding in trials included in systematic reviews and meta-analyses, and the new TACIT tool is being developed by the Cochrane Collaboration to supplement its risk of bias tool and to integrate considerations of FCOIs into bias assessment. We encourage uptake of both of these tools by journals and authors of systematic reviews and meta-analyses so that the potential influence of industry sponsorship and other author-industry ties can be considered by users of systematic reviews and meta-analyses.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13643-020-01318-5>.

Additional file 1: Methods 1. Title/Abstract and Full Text Eligibility Coding Guide.

Additional file 2: Methods 2. Meta-Analysis Data Extraction.

Abbreviations

FCOI: Financial conflicts of interest; RCT: Randomized controlled trial

Authors' contributions

BDT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MR, LAB, JL, EHT, and BDT contributed to the study concept and design. CB, MR, KAT, LB, JL, EHT, and BDT contributed to the acquisition, analysis, or interpretation of data. CB, KAT, and BDT drafted the manuscript. CB, KAT, MR, LAB, JL, EHT, and BDT critically revised the manuscript for important intellectual content. BDT contributed to the statistical analysis. BDT supervised the study. The authors read and approved the final manuscript.

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Availability of data and materials

All data extracted during this study are provided in Tables 1, 2 and 3.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Dr. Bero disclosed that she is Senior Editor, Cochrane Public Health and Health Systems, for which the University of Sydney receives remuneration. All other authors declare that they have no competing interests.

Author details

¹Lady Davis Institute of the Jewish General Hospital, 4333 Cote Ste Catherine Road, Montreal, Quebec H3T 1E4, Canada. ²Department of Psychiatry, McGill University, Montreal, Quebec, Canada. ³Kingsway Medical Centre Family Health Organization, Toronto, Ontario, Canada. ⁴Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Camperdown, New South Wales, Australia. ⁵School of Health Policy and Management, York University, Toronto, Ontario, Canada. ⁶Emergency Department, University Health Network, Toronto, Ontario, Canada. ⁷Behavioral Health and Neurosciences Division, VA Portland Health Care System, Portland, Oregon, USA. ⁸Department of Psychiatry, Oregon Health & Science University, Portland, Oregon, USA. ⁹Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada. ¹⁰Department of Medicine, McGill University, Montreal, Quebec, Canada. ¹¹Biomedical Ethics Unit, McGill University, Montreal, Quebec, Canada. ¹²Department of Psychology, McGill University, Montreal, Quebec, Canada. ¹³Department of Educational and Counselling Psychology, McGill University, Montreal, Quebec, Canada.

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