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The evaluation of financial conflicts of interest in addiction medicine systematic reviews and meta-analysis

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Title: The evaluation of financial conflicts of interest in addiction medicine systematic reviews and meta-analysis

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Manuscript word count: 3316
Abstract word count: 271
Figures: 2
Tables: 5

Abstract:

Objective: To evaluate the quantity of conflicts of interest, the accuracy of authors self reporting them, and the effects on results favorability within addiction medicine systematic reviews.

Design: A search was performed on MEDLINE (Ovid) from January 2016 to April 25th, 2020 to locate systematic reviews and meta-analyses focused on treatments of addiction disorders using multiple search strings. Data was extracted from the article including conflict of interest statements, authorship characteristics, and favorability of the results/conclusion section. A systematic search pattern was used to identify any undisclosed conflicts of interest on the Open Payments Database, Dollars for Profs, Google/United states Patents, and prior conflict of interest statements in other published works.

Results: The search algorithm identified a total of 127 systematic reviews with 665 unique authors. Of the 127 studies, 81 reported no authors with conflicts of interest, 28 with 1 or more conflict, and 18 had no conflict of interest statement. Additional non-disclosed conflicts of interest were found on the Open Payments Database (10), Docs for Profs (1), registered patents (3), and PubMed searches of other authored publications (20). Of the 127 systematic reviews, the discussion and conclusion favored the treatment group in 53, were mixed in 47, 27 and favored the standard of care treatment. No statistically significant correlations were found between the favorability of the treatment recommendations and source of funding (0.822), affiliation of the first author (0.182), or affiliation of the last author (0.312).

Conclusion: Although multiple undisclosed financial conflicts of interest were found, there was no correlation with favorability of the results or discussion/conclusions in the addiction medicine systematic reviews.

Keywords: Psychiatry, Addiction Medicine, Conflicts of Interest, Bias, Evidence based medicine

Article Summary:
- Inclusion criteria included systematic reviews and meta-analysis in addiction medicine that were published between January 2016 to April 25th, 2020
- Articles were screened using Rayyan in a double blind fashion by abstract and then full-text to ensure they met inclusion criteria.
- A step-by-step systematic search algorithm was used to identify undisclosed conflicts of interest through the Open Payment Database, Dollars for Profs, Google/USPTO patents, and PubMed for other authored articles.
- Although our search pattern was broad with multiple screenings performed, there may be other systematic reviews or metaanalysis that were published during the period analyzed.
- Financial conflicts of interest is a prominent focus in research currently and continued studies should evaluate how they continue to change or address them in the future.

Introduction

In 2018, 20.3 million people were classified as having substance dependence or abuse[1], and during an 18 year period (1999 - 2018) more than 700,000 Americans died from overdose [2].The National Institute on Drug Abuse estimates that tobacco, alcohol, and illicit drug misuse results in roughly $740 billion spent on issues related to crime, unemployment and health care[3]. One compounding issue when assessing treatment options for individuals with substance abuse is the potential mental health aspects that may or may not be diagnosed.[4–7] Despite the large number of prevention and treatment programs implemented over the last 35 years and the billions of dollars spent to fund them[8], we are now faced with a major health crisis. The high prevalence of substance abuse, with the increasing mortality and morbidity that follows addiction prompts the need for sustainable and meticulously thorough research to guide treatment plans.[9]

When physicians make treatment decisions, they base them off of evidence-based clinical practice guidelines supported by systematic reviews. The American Society of Addiction Medicine's (ASAM) 2020 *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use[10]* provides recommendations for the use of pharmacological treatments including methadone, buprenorphine, and naltrexone. The ASAM used 35 systematic reviews in this updated guideline. The American Psychiatric Association (APA) also has a recently updated guideline alcohol use disorder citing 15 systematic reviews used in the rationale for treatment options[11].

The impact of systematic reviews have on clinical judgement and treatment regimens makes it imperative that they are regarded as accurate and all bias is controlled for or addressed. Industry sponsorship and conflicted authors have both been shown to result in bias affecting the results in numerous publications[12–14]. Andreatos and colleagues[15] found more than 87% of general payments to authors of clinical guidelines were inaccurately reported. Previously published literature has revealed the pervasiveness for conflicted authors in psychiatric trials and the association with positive outcomes.[16] With the negative effects that conflicts of interest have on publications outcomes, further research must be done to limit conflicts and increase accurate reporting when present.

The Sunshine Act which is a federal law that stemmed from a need for greater transparency regarding US physician disclosures such as honoraria, travel expenses and ownership.[17] The Open payments database contains information regarding the financial relationships between manufacturers of devices and pharmaceuticals with US based physicians. Researchers have previously used and continue to use open payments as a tool for cross referencing US based physician authors and their financial disclosure statements. [18–20] Databases such as ProPublica's Dollars for Profs provides a resource for searching the reported disclosures of PhDs who are employed through public universities. Given that bias of competing interest must be accounted for, this study aims to assess the accuracy of disclosure practices among authors of systematic reviews investigating treatments of addiction medicine. A systematic methodological approach is taken to thoroughly identify any conflicts of interest that may affect the outcome of reviews and the standard practice of medicine.

Methods

Transparency, Reproducibility, and Reporting

We have provided study materials and protocol on Open Science Framework to increase transparency and reproducibility of our results.[21] While drafting this paper, we referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[22] and Murad and Wang's guidelines for meta-epidemiological studies.[23]

Search strategy

We searched MEDLINE (Ovid) from January 2016 to April 25th, 2020 to locate systematic reviews and meta-analyses focused on treatments of addiction disorders using the search strategy provided in the online protocol.[21] The search results were then uploaded to a systematic review screening platform, Rayyan (https://rayyan.qcri.org/).

Screening

Two authors screened abstracts and titles regarding addiction in a masked, duplicate manner. Full-text articles were evaluated following title and abstract screening to determine final inclusion. Disagreements were discussed until a consensus was reached. Additional authors were available for third party arbitration.

Eligibility Criteria

We will use the PRISMA-P definition of a systematic review/meta-analysis, which states that a systematic review is "a review of a clearly formulated question that uses systematic and explicit methods to identify, select, critically appraise relevant research, and collect/analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies. Meta-analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies."[24].

To be included in this study, an article must be a systematic review or meta-analysis designed to address interventions for drug, alcohol or tobacco. Furthermore, to qualify for inclusion, systematic reviews must have been published between September of 2016 and the date which the search was conducted (April 25, 2020). We chose the pre-specified date range from September 2016 forward to allow 36 months from the time of the Open Payments Database which appeared online in September 2013. The date range (January 2016 to April 25th, 2020) was selected according to the International Committee of Medical Journal Editors' (ICJME) recommendation that any financial interests be disclosed up to 36 months prior to the time of journal submission.[25] We chose the pre-specified date range to allow 36 months from the time the search of MEDLINE was conducted as the Open Payments Database began publishing data from August 2013.

Only systematic reviews published in English and reviews which synthesize studies of human data will be included. The following study types will be excluded from our study: observational studies (case control, cohort, surveys), clinical trials, narrative reviews, systematic reviews not related to (1) drug, alcohol and tobacco addiction prevention, (2) stabilization following excessive use of a substance, (3) relapse prevention or (4) recovery maintenance, duplicates, withdrawn or retracted studies, non-human studies, systematic reviews without abstracts, letters to the editor, and any remaining study which does not meet the inclusion criteria.

Training

All investigators were required to complete online training modules, which provided an overview of the study design, objectives of the study, study materials, and examples of data extraction from systematic reviews. The training was recorded and is available online for reference.[21]

Data extraction

Two authors performed data extraction independently in a masked, duplicate fashion. Investigators extracted the following data items from each SR: (1) PubMed identification number and/or DOI; (2) journal name; (3) date of publication; (4) name of author(s); (5) affiliation(s) for the first and last author; (6) funding source; (7) complete COI statement; (8) whether the SR or meta-analysis addressed risk of bias (RoB); (11) the verbatim RoB statement; (12) whether author(s) were also an author on one or more of the primary studies included in the review (yes/no); (13) total number of self-cited primary studies; (14) primary outcome; and (15) whether narrative results and conclusions favored the treatment or comparison group (e.g., placebo, standard of care, control). We used the term "conclusion" to represent a combination of the discussion and conclusion section of included reviews. Funding source for the systematic review will be categorized as follows: industry, government, private non-profit, mixed, other, not funded, or not disclosed.

Favorability of narrative results and conclusions

Narrative results and conclusions were designated as "favorable", "unfavorable", or "mixed/inconclusive". To evaluate the favorability of results and conclusions, we defined a favorable result or conclusion as one where the authors of the systematic review directly stated or implied in the results or conclusion section that the experimental group was determined to be definitively or probably superior to the control group or placebo. An unfavorable result or conclusion was defined as one where the authors of the systematic review directly stated or implied that the experimental group was not superior to the control group or placebo. When appraising the results section, "favorable" was assigned to SRs with only positive results. "Unfavorable" was assigned when negative results were exclusively reported. "Mixed/inconclusive" was assigned to narrative results sections that included both positive and negative results with no clear interpretation of the results. When appraising the conclusion sections, "favorable" was assigned to when authors stated or implied favorability towards the target intervention. "Unfavorable" was assigned when authors stated or implied favorability towards the comparison or control group. When neither "favorable" nor "unfavorable" applied to the conclusion, "mixed/inconclusive" was assigned (i.e., reporting negative population outcome but positive subgroup analysis).

Identification of undisclosed COI

Searches for undisclosed COI were undertaken using the algorithm provided in Figure 1. This stepwise search was based on the methodology provided by Mandrioli et al.,[12] with modifications. These modifications included the incorporation of 3 additional databases — the Open Payments database, Dollars for Profs, and the United States Patent and Trademark Office (USPTO). To ensure consistency between investigators, authors created standardized search strings for PubMed, USPTO Database, and Google Patents using the Python programming language (Python Software Foundation, https://www.python.org/). If we were unable to verify a

patent belonged to the author, we considered the search inconclusive and continued our process. In accordance with ICMJE standards of COI disclosure, PubMed searches were limited to 36 months prior to the publication of the original SR to determine if previously published studies included additional COI not disclosed in the SR from our sample. If this search yielded more than 20 publications, each investigator individually assigned random numbers to the resulting publications. The COI statement of the first 20 studies numerically were then examined. Each investigator individually generated random numbers to include wider search of publications and opportunities for authors to disclose a COI. This process was performed until an undisclosed COI was discovered, at which time the author was then counted as having an undisclosed COI. This stop-procedure is identical to that used by Mandrioli et al.[12]

Risk of bias evaluations
To evaluate the risk of funding bias, we applied the Cochrane Collaboration's criteria for assessment, and the following 4 items from Mandrioli et al[12]: (1) whether explicit and "well defined" criteria that could be replicated by others were used to select studies for inclusion/exclusion; (2) whether an adequate study inclusion method, with two or more assessors selecting studies, was used; (3) whether search strategies were comprehensive; and (4) whether methodological differences that may introduce bias were controlled for. Each item was designated as yes, no, or unclear. We considered the overall RoB to be low if at least 3 of the aforementioned criteria were sufficiently met. Otherwise, the RoB was considered to be high. Authors S.D. and S.S. performed an independent and masked evaluation of risk of bias items. Discrepancies were discussed between investigators until a consensus was reached. D.T. and M.V. were available for third party adjudication.

Statistical Analysis
Results were quantified using descriptive statistics, and relationships were evaluated by Fisher's exact tests, when possible. Stata 16.1 (StataCorp, LLC, College Station, TX) was used for all analyses.

Patient and Public Involvement
Patients and the public were not involved in the development of the research design or question addressed in this study. This study evaluated systematic reviews, meta-analysis, and the authors of such publications. No patients or health information was used in this study.

Ethics Approval
An institutional review board and ethics review was not required as there were no animal or human subjects involved in this research study.

Results
Sample Characteristics
A total of 1331 manuscripts published between January 2016 and April 25th 2020 were identified using the search string listed in online materials. Of the initial sampling, two researchers reviewed each through rayyan.com and determined that 321 met the inclusion criteria. Of the 321 initially included publications, 194 were excluded after a full text review. The reasons for exclusion included 62 being outside the date range, 43 not being a systematic review, 27 being a published poster/abstract, 59 did not address the 4 treatment areas of

addiction evaluated here, and 3 were inaccessible even after interlibrary loan request. A final number of 127 publications were evaluated for authors with financial conflicts of interest (Figure 1).

The journals with the most publications analyzed include *Addiction* (30*), Drug and Alcohol Dependance* (18), *Addictive Behaviors* (14), *Journal of Substance Abuse Treatment* (14), *and Nicotine & Tobacco Research* (12). The interventions used in each publication includes pharmacological (64), behavioral therapy/psychosocial treatments (53), prevention of addiction (8), and procedures (2).

Conflicts of Interest Statements within Publications
Of the 127 systematic reviews or meta-analyses identified , 28 contained a statement reporting 1 more conflict of interest, 81 reported no authors with conflicts of interest, and 18 provided no conflict of interest statement. Public funding was the most commonly reported with 66 of the 131 publications compared to university (4), public & university (3), and private/industry (2). Furthermore, 33 declined receiving any funding and 19 did not have a statement addressing funding (Table 1).

Author Specific Conflicts of Interest
Of the 127 systematic reviews analyzed, 655 total authors were identified. The most common countries of origin included the United States (276), United Kingdom (116), Canada (69), and Australia (61). Publications listed 103 of the 655 authors as having a conflict of interest. By searching the Open Payments database, 21 authors had profiles, 15 reported receiving financial payments, and 10 of authors receiving funding did not report it as specified by *ICMJE* standards. Additional undeclared conflicts of interest were identified on Docs for Profs (1), registered patents (3), and PUBMED searches of other authored publications (20) (Table 2).

Favorability of results or discussion/conclusion related to conflicts of interest
Of the 127 systematic reviews, the discussion and conclusion favored the treatment group in 53, were mixed in 47, 27 and favored the standard of care treatment. There was no statistically significant relationship between favorability of results and author funding source (p= 0.251), first author affiliation (p= .0431), and last author affiliation (p= 0.684). Additionally No statistically significant correlations were found between the favorability of the discusson/conclusions and source of funding (0.822), affiliation of the first author (0.182), or affiliation of the last author (0.312) (Table 3 - 5).

Discussion
In our study, we did not note a relationship between conflicted authors and the nature of the results and conclusions of systematic reviews. Continued research into conflicts of interest and the effects they have on study outcomes is important. Multiple publications have found that authors that receive funding from pharmaceutical companies are more favorable with the reporting of results and recommendations than research performed independently[12,26,27]. In our case, no relationship was found between conflicts of interest and favorability of results but our limited sample size of eligible authors may cause uncertainty in this finding. After having performed this study, we advocate for a larger sample of systematic reviews with more authors

who meet eligibility criteria to draw more definitive conclusions about the extent to which conflicted authors influence systematic review outcomes.

Although there was not a correlation between the result findings and conflicts of interest, there were still a large number that did not appropriately disclose. Of the 655 authors, 105 (16%) had an undisclosed conflict, which represents nearly 1-in-6 authors. One-quarter of all authors were found to have some conflict of interest either accurately disclosed or discovered upon our systematic search of authors. We presume that the true number of authors with undisclosed conflicts of interest is underestimated, since only US physician researchers have a legal responsibility to list financial support on the Open payments website. Thus, non-US authors may have undisclosed conflicts that were not findable through our searches. This finding concerns us, as a large and consistent body of evidence indicates that self-disclosure is inaccurate. For example, Wayant et al., reported that approximately one-third of oncologist authors of pivotal cancer therapy trials (i.e., establishing the basis for drug approval) did not disclose financial conflicts with the industry sponsor. We believe that transparency and third party reporting structures are necessary to successfully mitigate this issue. It is therefore critical to think about alternative reporting mechanisms to improve public trust in science and for readers of research studies to be able to critically evaluate the likelihood of financial bias on decision making, results, and discussions.

Another concerning finding is that authors who referenced their own papers in the systematic review were more likely to have an undisclosed conflict of interest. Self-citations increase important research metrics, such as the h-index (for some calculations) and the number of citations received by the author. Thus, there may be possibilities where authors may selectively favor their own studies for inclusion in systematic reviews. There are potentially countless reasons for self-citation that could include increasing one's academic profile or increasing the impact of previous research. We acknowledge that determining which characteristics might contribute to these relationships between undisclosed conflict of interest and self-citations is outside the scope of our current investigation. Additionally, authors of systematic reviews may be experts in their field or perform research on a narrow topic. These authors may be appropriate when performing a systematic review but should be forward about their inclusion of their own research and address any other potential bias that may stem from it. Future research that expands upon this finding is warranted and encouraged.

Although these findings demonstrate no relationship between conflicts of interest and addiction medicine systematic review favorability, it is still important to improve reporting and limit possible opportunities in the future. The author guidelines section of the top 5 psychiatry journals based on Google Scholar metrics was performed. These journals included *Biological Psychiatry, JAMA psychiatry, Molecular Psychiatry, American Journal of Psychiatry,* and *The Lancet Psychiatry* all require an accurate statement for individual authors on a publication. The requirements for these statements are very specific but there is no mention of verifying the information reported. We recommend that journals implement a screening protocol to search the Open Payments database at the very least for possible undisclosed conflicts of interest. Regarding database selection to uncover undisclosed conflicts, PubMed produced the greatest yield. The Open Payments Database is desirable because the data contained within it are not self-disclosed; however, only healthcare workers are currently listed. Many authors of

systematic reviews are not health care workers; instead, they are methodologists, epidemiologists, scientists, research assistants, or students. In these cases, Open Payments will not provide a significant yield. In an effort to include non-physician scientists in our search, we used Dollars for Profs, which was created by ProPublica from NIH COI records. Again, this database is limited to author self-disclosure. It yielded little return and may not be worth considering in future investigations. Likewise, our patent searches generated very few returns. Searching patent databases such as 'Google patents' for discrepancies in disclosure statements has been previously verified as a valid tool for locating undisclosed patents.[29] The use of the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM) for examining consistency in authors' disclosure statements between separate publications has previously been validated as a source for identifying discrepancies.[30].

Strength and limitations
This study was subject to both strengths and limitations. Regarding its strengths, our study was performed in duplicate across screening and data extraction phases by two of the authors who were masked throughout. Performing the study in duplicate limits errors in data extraction and errors in study selection. This process is considered the gold standard methodology of the Cochrane Collaboration[28]. We performed this study according to a previously developed and published protocol, and any deviations to our protocol were described in subsequent protocol updates. Regarding its limitations, we may have not included relevant systematic reviews or our searches may not have retrieved all relevant systematic reviews. Furthermore, there is always the possibility that the authors who performed data extraction exercised some degree of subjectivity, especially related to whether a systematic review conclusion favored the intervention or not. Sample size in our study is also a limitation. Studies with larger sample sizes are needed, or perhaps, a meta-analysis of existing studies would garner the power necessary to provide a more informed understanding of whether authors with COIs are more likely to report results and conclusions favoring the intervention.

Conclusion:
Our study found that there was no relationship between authors with conflicts of interest and the favorability of the systematic review discussion/conclusion. Although there was no correlation, we did identify 105 authors with undisclosed financial conflicts of interest.

Data statement
The data used in this study is available at a supplementary file.

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Table 1: Characteristics of included systematic reviews and meta-analysis

Characteristic	Form Response	N (%)
Journal in which systematic reviews were published **(n= 127)**	Addiction	30 (23.6)
	Drug and Alcohol Dependance	18 (14.2)
	Addictive Behaviors	14 (11.0)
	Journal of Substance Abuse Treatment	14 (11.0)
	Nicotine and Tobacco Research	12 (9.4)
	Alcohol and Alcoholism	6 (4.7)
	Other*	33 (26.0)
Conflict of Interest Statement (n=127)	All authors report no COI	81 (63.8)
	No COI statement present	18 (14.1)
	One or more authors report a COI	28 (22.0)
Intervention Type (n= 127)	Pharmacologic	64 (50.4)
	Procedure	2 (1.6)
	Behavioral Therapy/Psychosocial treatments	53 (41.7)
	Prevention	8 (6.3)
Affiliation of First Author (n= 127)	Public Academic Institution	92 (72.4)
	Private Academic Institution	15 (11.8)
	Government	14 (11.0)
	Public academic institution, government	1 (0.8)
	Non-profit institution	4 (3.1)
	Private-for-profit	1 (0.8)

Affiliation of Last Author (n= 127)	Public Academic Institution	94 (74.0)
	Private Academic Institution	15 (11.8)
	Government	13 (10.2)
	Public academic institution, government	1 (0.8)
	Non-profit institution	3 (2.4)
	Private-for-profit	1 (0.8)
Source of Funding (n= 127)	No funding received	33 (26.0)
	No statement listed	19 (15.0)
	Private/Industry	2 (1.6)
	Public	66 (52.0)
	University	4 (3.1)
	Public and University	3 (2.4)
Self-citation of primary studies (n=127)	No, did not include self-cited primary studies	109 (85.8)
	Yes, included one or more self-cited primary studies	18 (14.2)

Table 2: Characteristics of systematic review authors (n= 655)

	Reported conflict of interest	103 (81.1)
Accuracy of author COI disclosure statement (n= 655)	Undisclosed FCOI found on Open Payments database	10 (7.9)
	Undisclosed FCOI found on Docs for Profs	1 (0.8)
	Undisclosed FCOI found by patents	3 (2.4)
	Undisclosed FCOI found on PubMed	71 (55.9)
	Additional FCOI besides what is already declared	20 (15.7)
	United States	276 (42.1)
	United Kingdom	116 (17.7)
	Canada	69 (10.5)
	Australia	61 (9.3)
	India	17 (2.6)
	Netherlands	16 (2.4)
Country of affiliation for authors conducting the systematic review (n= 655)	Germany	15 (2.3)
	China	13 (2.0)
	Ireland	11 (1.7)
	Malaysia	11 (1.7)
	Switzerland	9 (1.4)
	France	7 (1.1)
	Belgium	6 (0.9)
	Spain	6 (0.9)
	Other	22 (3.4)

Table 3. Frequency of favorability of results and conclusions by funding sponsor

Review Outcome	Funding Sponsor							
	No funding received (n= 33)	No statement listed (n= 19)	Government (n= 1)	Private/ Industry (n= 2)	Public (n= 65)	University (n= 4)	Public/ University (n= 3)	Fisher's Exact
Favorability of Results								
Results Favor Treatment Group	7	5	0	0	18	2	2	
Results are Mixed/Inconclusive	17	11	1	1	33	2	1	
Results Favor Placebo or Control Group	9	3	0	1	14	0	0	P= 0.879
Favorability of Discussion/Conclusions								
Discussion Favors Treatment Group	15	7	0	0	27	2	2	
Discussion is Mixed/Inconclusive	11	10	1	1	22	1	1	
Discussion Favors Placebo or Control Group	7	2	0	1	16	1	0	P= 0.822

Table 4: Favorability of results and discussion/conclusion in relation to first author affiliation

Review Outcome	Affiliation						Fisher's Exact
	Government (n= 14)	Non-profit Institution (n= 4)	Private academic (n= 15)	Private for profit (n= 1)	Public academic (n= 92)	Public academic, government (n= 1)	
Favorability of Results							
Results Favor Treatment Group (n= 34)	2	0	5	0	27	0	
Results are Mixed/Inconclusive (n= 66)	9	3	9	1	44	0	
Results Favor Placebo or Control Group (n= 27)	3	1	1	0	21	1	P= 0.493
Favorability of Discussion/Conclusions							
Results Favor Treatment Group (n=53)	3	0	7	0	43	0	
Results are Mixed/Inconclusive (n= 47)	8	2	6	1	30	0	
Results Favor Placebo or Control Group (n= 27)	3	2	2	0	19	1	P= 0.684

Table 5: Favorability of results and discussion/conclusion in relation to last author affiliation

Review Outcome	Affiliation						
	Government (n= 13)	Non-profit Institution (n= 3)	Private academic (n= 15)	Private for profit (n= 1)	Public academic (n= 92)	Public academic, government (n= 1)	Fisher's Exact
Favorability of Results							
Results Favor Treatment Group (n= 34)	4	0	5	0	25	0	
Results are Mixed/Inconclusive (n= 66)	7	2	9	1	47	0	
Results Favor Placebo or Control Group (n= 27)	2	1	1	0	22	1	P= 0.684
Favorability of Discussion/Conclusions							
Results Favor Treatment Group (n=53)	4	0	8	0	41	0	
Results are Mixed/Inconclusive (n= 47)	7	1	5	1	33	0	
Results Favor Placebo or Control Group (n= 27)	2	2	2	0	20	1	P= 0.312

Figure 1: Search pattern to identify undisclosed financial conflicts of interest

Figure 2: Stepwise progression of search strategy to identify SR/MA and authors in addiction medicine.

Figure 1: Search pattern to identify undisclosed financial conflicts of interest
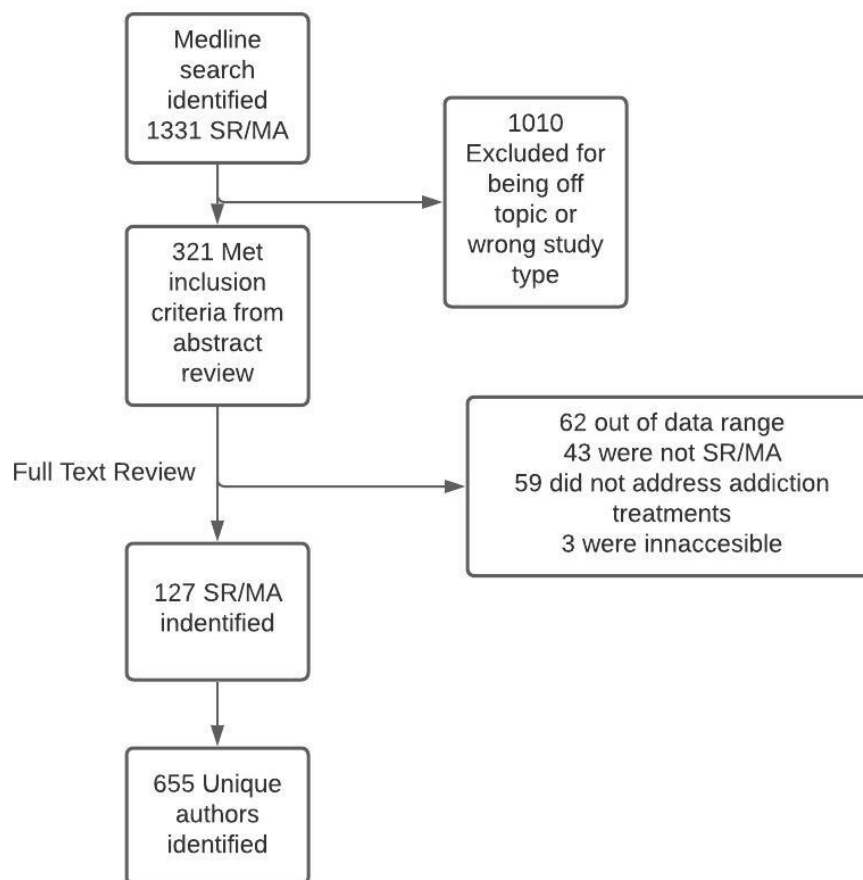
141x257mm (72 x 72 DPI)

Figure 2: Stepwise progression of search strategy to identify SR/MA studies and authors in addiction medicine.

139x134mm (160 x 160 DPI)

Title of Artic	PMID or DC	Name of Jc	Date of Pub	List the nar	List of Auth	Affiliation o	Affiliation o	Is there a fu
Evidence F	29370431	Nicotine & `	06/2019	Tobacco pc	Natalie Pap	Public acac	Public acac	Yes
Improving h	30684819	Addictive B	06/2019	interventio	Yael Bar-Z(	Public acac	Public acac	Yes
Systematic	31302311	Addictive B	11/2019	mutual sup	Elizabeth D	Public acac	Public acac	Yes
A systemat	26355397	Addictive B	01/2016	nicotine rep	Jessica L K	Governmer	Governmer	Yes
Effectivene	26687544	Addiction	05/2016	motivationa	Lili Li 1, Sh	Public acac	Public acac	Yes
Use of Vare	25646351	Nicotine & `	01/2016	Varenicline	Jessica Scl	Private aca	Private aca	Yes
A Systemat	26069036	Nicotine & `	05/2016	smoking ce	Sarah L. Th	Public acac	Public acac	Yes
Peer-led int	26518976	Addiction	03/2016	Peer-led in	MacArthur	Public acac	Public acac	Yes
Topiramate	26826006	Addiction	08/2016	Topiramate	Mohit Singh	Public acac	Public acac	Yes
The efficacy	29248863	Addictive B	04/2018	computeriz	Alexandre (	Public acac	Public acac	Yes
Gender and	29364763	Substance	08/2018	Substance	Luis A Vald	Public acac	Public acac	Yes
Baclofen: it	29479827	Addiction	08/2018	Baclofen	Abigail K R	Public acac	Public acac	No
Parent-bas	30096640	Drug and A	11/2018	Parent-bas	Ai Bo 1, Au	Public acac	Public acac	Yes
The efficacy	30506845	Addiction	04/2019	nicotine rep	Maxwell Ol	Private aca	Private aca	Yes
Group treat	30797382	Journal of S	04/2019	Group treat	Gianluca L(	Public acac	Public acac	Yes
Effectivene	30797392	Journal of S	04/2019	Methadone	Kelly E Mo	Public acac	Private aca	Yes
A systemat	30831429	Drug and A	04/2019	buprenorph	Sara Ling 1	Public acac	Public acac	Yes
Effectivene	30957142	Alcohol and	05/2019	Workplace	K Yuvaraj 1	Public acac	Public acac	Yes
Telemedicii	31006553	Journal of S	06/2019	Telemedicii	Lewei Allis(	Public acac	Public acac	Yes
The Cochra	31062859	Alcohol and	07/2019	Brief interv	F.R. Beyer	Public acac	Public acac	Yes
A meta-ana	31077485	Addiction	05/2019	gabapentin	Henry R Kr	Private aca	Private aca	Yes
Short- and	31112834	Drug and A	07/2019	digital prev	Nikolaos B(	Public acac	Public acac	Yes
Pharmacotl	31328345	Addiction	12/2019	Pharmacotl	Brian Chan	Public acac	Public acac	Yes
The efficacy	31349206	Drug and A	09/2019	spiritual/reli	Audrey Har	Public acac	Public acac	Yes
The Efficac	31557336	Alcoholism:	09/2019	Technology	Audrey Har	Public acac	Public acac	No
A meta-ana	31599606	Journal of (	12/2019	cognitive-b	Molly Magil	Governmer	Private aca	Yes
Efficacy an	31678838	Drug and A	12/2019	varenicline	Awirut Oon	Public acac	Public acac	Yes
Psychologi(	31856953	Journal of S	02/2020	Psychologi(	Alexandra I	Public acac	Public acac	Yes
Acceptabilit	31863669	Addiction	01/2020	naltrexone	Anees Bah	Public acac	Public acac	No
Clinical ber	31978670	Drug and A	03/2020	NMDAR an	Author links	Private aca	Private-for-	Yes
Brief interv	31985127	Addiction	02/2020	Behaviour (	Tom Lynch	Public acac	Public acac	Yes
Brief Interv	32012140	Journal of /	01/2020	Brief Interv	Sameer Im	Public acac	Public acac	Yes
Efficacy an	26594837	Addiction	04/2016	pharmacotl	Emmert Ro	Public acac	Public acac	No
Meta-analy	26637990	Addiction	05/2016	brief interv	Christiane (	Public acac	Public acac	Yes
Positive you	26874990	Internationa	10/2016	youth deve	G J Melend	Public acac	Public acac	Yes
Acupunctur	26968093	Drug and A	06/2016	Acupunctur	Sean Grant	Non-Profit i	Non-Profit i	Yes
Re-starting	26990248	Addiction	06/2016	Smoking ce	Matthew Jo	Public acac	Public acac	Yes
Varenicline	27043328	Addiction	06/2016	Varenicline	Qi Wu 1, Si	Public acac	Public acac	Yes
Digital Inter	27160333	European A	08/2016	Digital Inter	Eva Hoch 1	Public acac	Public acac	Yes
Efficacy of	27567270	Alcohol and	08/2016	Motivationa	Jaison Jose	Public acac	Public acac	No
Sex Differe	27613893	Nicotine & `	03/2017	Pharmacotl	Philip H Sm	Private aca	Private aca	Yes
Internet inte	28295758	Addiction	09/2017	Internet int	Nikolaos B(	Public acac	Public acac	No
A systemat	28334456	Drug and A	05/2017	combined s	Nicola C N(	Governmer	Governmer	Yes
Follow-up t	28437121	Psychology	04/2017	Motivationa	Caitlin S. S	Public acac	Public acac	No
Pharmacok	28940866	Addiction	02/2018	nalmefene,	Clément Pa	Governmer	Governmer	Yes
Brief interv	31751868	Drug and A	11/2019	Brief interv	Jillian Halla	Public acac	Public acac	Yes
Group-base	29195596	Journal of S	01/2018	buprenorph	Randi Sokc	Private aca	Private aca	No
A systemat	32003088	Addiction	01/2020	interventior	Hannah Wa	Public acac	Public acac	No
Interventior	30502543	Drug and A	01/2019	pharmacolc	Rod Knight	Public acac	Public acac	Yes
Are Electro	29608714	Nicotine & `	04/2019	Electronic (	Sarah Gent	Public acac	Public acac	Yes
Beyond fac	28554033	Addictive B	10/2017	alternative	Shan Jiang	Public acac	Public acac	Yes
The effectiv	26790691	The Interna	02/2016	drug deten	D Werb 1, /	Governmer	Governmer	Yes
Are brief al	28750345	Drug and A	09/2017	brief alcohc	A M Dohert	Public acac	Public acac	Yes
Primary ca	29040331	PLoS One	10/2017	MAT, bupre	Pooja Lagis	Public acac	Governmer	Yes
Systematic	https://journ	Canadian J	02/2016	naloxone a	Main, Fiona	Public acac	Public acac	Yes

Systematic	29733380	Nicotine & T	07/2019	Education,	Cheneal Pu	Public acac	Public acac	Yes
Integrating	29920839	Addiction	12/2018	Smoking ce	Eliza Skeltc	Public acac	Public acac	Yes
Evidence fc	31585357	Drug and A	11/2019	1) state leg	Tamara M I	Governmer	Public acac	Yes
Efficacy of	30165705	Nicotine & T	10/2019	Nicotine pa	Seung-Kwc	Public acac	Public acac	Yes
Effect of As	30699412	European A	02/2019	assertive cc	Louise Pen	Public acac	Public acac	No
Adjunctive	31757263	Journal of S	12/2019	memantine	Author links	Governmer	Governmer	Yes
Use of Men	31204787	Nicotine & T	03/2020	Menthol cig	Philip H Sm	Public acac	Public acac	Yes
Occupation	26738639	Journal of S	03/2016	Occupation	Sally Wasn	Public acac	Public acac	No
A Systemat	26808307	Journal of A	03/2016	Psychosoci	Karen Dug	Governmer	Governmer	Yes
Combinatio	26809272	The Americ	01/2016	bupropion S	Tiffany Vog	Public acac	Public acac	No
Naloxone w	26996745	Drug and A	06/2016	Naloxone	John Stran	Public acac	Public acac	Yes
Mobile tech	27310031	Addictive B	11/2016	Mobile tech	Lauren A F	Private aca	Private aca	Yes
Community	27325204	Drug and A	05/2017	Community	ABHIJIT N/	Public acac	Public acac	No
Personalizi	27515725	Drug and A	10/2016	Personalize	Rachel L. T	Public acac	Public acac	Yes
Smoking Cc	27613909	Nicotine & T	11/2017	Smoking ce	Israel Berg	Public acac	Public acac	Yes
A Systemat	28247556	Alcoholism:	03/2017	Naltrexone	Shantrel S	Public acac	Public acac	Yes
Modafinil Tr	28350194	Substance	08/2017	Modafinil	Dinesh Sar	Non-Profit i	Public acac	No
Psychosoci	28554034	Addictive B	11/2017	providing ii	Anil Rane 1	Governmer	Governmer	Yes
Treatment f	29136566	Drug and A	01/2018	any interve	Anne Marie	Public acac	Public acac	Yes
Treatment c	29145545	Alcohol and	05/2018	antipsychot	Barkat Mas	Public acac	Public acac	Yes
Duration of	29195594	Journal of S	01/2018	psychosoci	Lotte Kram	Public acac	Public acac	Yes
Diminishing	29377409	Addiction	05/2018	Bupropion	Laura J Ro	Public acac	Public acac	Yes
Applications	29421343	Addictive B	06/2018	virtual realit	Alexandra (	Public acac	Public acac	Yes
Parenting c	29706173	Journal of S	06/2018	parenting ir	Angela D M	Public acac	Public acac	Yes
Review: Ad	29906718	Drug and A	08/2018	benzodiaze	Justine W.\	Private aca	Private aca	Yes
A Meta-Ana	30422781	Journal of S	09/2018	Computer-I	Hayley A C	Public acac	Public acac	No
Modelling c	30614586	Addiction	05/2019	pharmacolc	Sarah E Ja	Public acac	Public acac	Yes
A systemat	30731328	Addictive B	05/2019	behaviour c	Tracey J Br	Public acac	Public acac	Yes
Naltrexone	31148304	Addiction B	11/2019	Naltrexone	Lara A Ray	Public acac	Public acac	Yes
Mobile tele|	31265747	Addiction	11/2019	Mobile tele|	Carol-Ann (	Public acac	Public acac	Yes
A systemat	31370989	Journal of S	09/2019	Behavioral	Tera L Faz:	Public acac	Public acac	Yes
Dropout rat	31454123	Addiction	02/2020	retention ra	Sara N. Lap	Public acac	Public acac	Yes
Technology	31566787	Alcoholism:	09/2019	echnology-	Brian D. Kil	Private aca	Private aca	Yes
Youth Parti	31596160	Substance	10/2019	Youth parti	Elizabeth S	Public acac	Public acac	Yes
Review of I	31782349	Substance	11/2019	Individual p	Jennifer Ha	Public acac	Public acac	No
A review of	32036191	Addictive B	06/2020	nonpharma	Alaina Mart	Public acac	Public acac	No
Behaviour c	32196796	Addiction	04/2020	Behavior C	Nicola Blac	Public acac	Public acac	Yes
Preventing	32197211	Addictive B	03/2020	EEG-neuro	Clémence I	Public acac	Public acac	Yes
Opioids on	10.1097/C>	Canadian J	03/2018	Naloxone,	Bahji, Anee	Public acac	Public acac	Yes
Treatment c	https://journ	Canadian J	12/2016	cannabis u:	Dr. Anees I	Public acac	Public acac	Yes
A systemat	https://www	HEROIN Al	11/2019	methadone	Nur Azlina	Public acac	Public acac	Yes
A Meta-Ana	29059419	Nicotine & T	11/2018	Brief tobac	Jennifer M.	Governmer	Governmer	Yes
Smoking Cc	28857640	Substance	01/2018	nicotine rep	Anne Yee 1	Public acac	Public acac	No
Effects of re	31328353	Addiction	12/2019	transcrania	Jack J Q ZI	Public acac	Public acac	Yes
Electronic (	27113014	Nicotine & T	10/2016	Electronic (	Muhannad	Public acac	Public acac	Yes
Pharmacotl	30173086	Drug and A	11/2018	methylpher	Nicole K Le	Governmer	Public acac	Yes
Behavioral	31251347	Nicotine & T	06/2019	Behavioral	Suzanne T:	Governmer	Governmer	Yes
The effectiv	31254749	Drug and A	08/2019	residential	Dominique	Public acac	Public acac	Yes
Exposure tc	32079562	Journal of S	02/2020	Digital Marl	Jonathan K	Private aca	Private aca	Yes
What parer	28237717	Addictive B	07/2017	parenting s	Marieke Hic	Public acac	Public acac	Yes
Systematic	25866929	Drug and A	03/2016	Alcohol inte	Tyler B Wra	Private aca	Private aca	Yes
A Systemat	26482134	Journal of S	02/2016	Brief Interv	Meredith S	Public acac	Public acac	No
Peer-Delive	26882891	Journal of S	04/2016	Peer-Delive	Ellen L Bas	Private aca	Governmer	No
Are take-hc	27028542	Addiction	03/2016	naloxone	Rebecca M	Public acac	Public acac	No
Buprenorph	27223595	Addiction	12/2016	Buprenorph	Barbara K :	Private-for-	Public acac	Yes
Tincture of	27740713	Addiction	12/2016	opium tinct	Mohammac	Public acac	Public acac	Yes

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Does Indus	27864186	Alcohol and	11/2016	Alcohol Ma	Stephanie S	Governmer	Governmer	Yes
Efficacy of	28126511	Addictive B	06/2017	mindfulnes	Margaret A	Non-Profit i	Non-Profit i	Yes
Mindfulnes	28153483	Journal of S	04/2017	Mindfulnes	Wen Li 1, N	Public acac	Public acac	No
Culturally s	28237051	Journal of S	04/2017	culturally s	Katarzyna	Private aca	Public acac	Yes
Substance	28318279	Psychology	05/2017	Non-college	Jordan P. D	Public acac	Public acac	No
Systematic	28499259	Addictive B	05/2017	Social Med	John A Nas	Private aca	Private aca	Yes
Contingenc	28688295	Drug and A	09/2017	Contingeno	Tom S Ains	Public acac	Public acac	Yes
Mindfulnes	28727663	Journal of A	09/2017	Mindfulnes	Sean Grant	Non-Profit i	Non-Profit i	Yes
Efficacy of	28805271	Drug and A	08/2017	Different int	Hélène Sim	Public acac	Public acac	Yes
Extended-r	29396985	Addiction	07/2018	Naltrexone	Brantley P.	Public acac	Public acac	Yes
A systemat	29750413	Alcohol and	07/2018	brief interv	Dorothy Ne	Public acac	Public acac	Yes
Whole-of-c	29806876	Addiction	11/2018	whole-of-cc	Emily Stock	Governmer	Governmer	Yes
AA attenda	29845709	Addiction	11/2018	AA attenda	J Scott Ton	Public acac	Private aca	Yes
Youth Cogr	32079560	Journal of S	03/2020	Alcohol Prc	Elizabeth R	Public acac	Public acac	Yes
Association	32196794	Addiction	04/2020	Solitary drir	Carillon J. S	Private aca	Private aca	Yes
Effectivene	http://www.	HEROIN AI	04/2017	methadone	Des Crowle	Public acac	Public acac	Yes

Funding Sc	Copy and p	Is a conflict	About the C	Copy and p	Do the auth	Complete s	Recode RC	Favorability
Public	This study i	Yes	Reports no	None decla	Yes	In order to a	?	Mixed (Neg
Public	This work v	Yes	Includes 1	Bar-Zeev Y	Yes	Quality of ir	?	Mixed (Neg
Public	This resear	Yes	Reports no	The author	Yes	Each article	?	Unfavorable
No funding	na	Yes	Reports no	none	Yes	Methodolog	?	Mixed (Neg
University	The study v	Yes	Reports no	none	Yes	To enable a	?	Mixed (Neg
No funding	none	Yes	Reports no	none	Yes	We assess	Cochrane F	Favorable (
Public	UK Centre	Yes	Reports no	None	Yes	Quality ass	Cochrane F	Favorable (
Public	This work v	Yes	Includes 1	R.C. is a Di	Yes	Risk of bias	Cochrane F	Mixed (Neg
Public	The author	Yes	Reports no	Declaration	Yes	Study quali	Cochrane F	Unfavorable
Public	This study v	Yes	Reports no	All of the ot	Yes	The metho	Cochrane F	Favorable (
No funding	The author	No	There is no	None	Yes	Risk of bias	Cochrane F	Mixed (Neg
No statema	na	Yes	Reports no	no conflicts	Yes	We examir	Cochrane F	Mixed (Neg
No funding	none	Yes	Reports no	none	Yes	Included st	Cochrane F	Unfavorable
Public	This work v	Yes	Includes 1	B.H. has se	Yes	The quality	Cochrane F	Mixed (Neg
Public	This study v	No	There is no	None	Yes	The Cochra	Cochrane F	Mixed (Neg
Public	This work v	No	Includes 1	Kelly E Mo	Yes	The Cochra	Cochrane F	Mixed (Neg
No funding	This resear	Yes	Includes 1	Dr. Kristin (	Yes	The quality	Cochrane F	Mixed (Neg
No funding	none	Yes	Reports no	none	Yes	Two indepe	Cochrane F	Favorable (
Public	Funding: Tl	Yes	Includes 1	Dr. Lin serv	Yes	Potential ris	Cochrane F	Mixed (Neg
No funding	This Cochra	Yes	Includes 1	Nicolas Bei	Yes	Where data	Cochrane F	Favorable (
Public	Dr. Kranzle	Yes	Includes 1	Disclosure:	Yes	We used th	Cochrane F	Unfavorable
No funding	None	Yes	Reports no	NOne	Yes	The validity	Cochrane F	Mixed (Neg
Public	This resea	Yes	Includes 1	This resear	Yes	Two review	Cochrane F	Unfavorable
No funding	No Funding	Yes	Reports no	None	Yes	Two review	Cochrane F	Mixed (Neg
No statema	na	Yes	Reports no	The author	Yes	Two review	Cochrane F	Unfavorable
Public	This resear	No	Includes 1	#AA02600	Yes	study-level	Cochrane F	Mixed (Neg
University	This work v	Yes	Includes 1	Srisurapan	Yes	Both autho	Cochrane F	Mixed (Neg
No funding	na	Yes	Reports no	na	Yes	The Cochra	Cochrane F	Favorable (
No statema	na	Yes	Reports no	none	Yes	We assess	Cochrane F	Unfavorable
No funding	Role of Fur	Yes	Reports no	Conflict of I	Yes	Several sea	Cochrane F	Mixed (Neg
Public	T.L. was su	Yes	Reports no	None.	Yes	Data extrac	Cochrane F	Favorable (
No funding	The presen	Yes	Includes 1	interest: J.F	Yes	For all inclu	Cochrane F	Unfavorable
Public	Funding fro	Yes	Includes 1	ER has not	Yes	Two author	Cochrane F	Favorable (
Public	This work v	Yes	Reports no	none	Yes	To investig	Cochrane F	Mixed (Neg
Public	This projec	Yes	Reports no	None decla	Yes	We conduc	Cochrane F	Unfavorable
Public	Role of Fur	Yes	Includes 1	SG's fiancé	Yes	The two rev	Cochrane F	Mixed (Neg
Public	This work v	Yes	Includes 1	We have re	Yes	Quality ass	Cochrane F	Unfavorable
Public	This work v	Yes	Reports no	none	Yes	Studies me	Cochrane F	Mixed (Neg
Public	This study v	Yes	Reports no	The author	Yes	In the conte	Cochrane F	Favorable (
No statema	na	Yes	Reports no	None decla	Yes	An assessr	Cochrane F	Mixed (Neg
Public	Funding wa	Yes	Includes 1	PHS and S	Yes	For risk ass	Cochrane F	Mixed (Neg
No statema	na	Yes	Reports no	none	Yes	The validity	Cochrane F	Mixed (Neg
Public	NN and LS	Yes	Includes 1	IK led the d	Yes	Risk of bias	Cochrane F	Unfavorable
No statema	na	No	There is no	None	Yes	Study quali	Cochrane F	Mixed (Neg
Public	Rennes CH	Yes	Includes 1	None. All a	Yes	Two review	Cochrane F	Mixed (Neg
Public	This resear	Yes	Includes 1	No conflicts	Yes	Risk of bias	Cochrane F	Mixed (Neg
No statema	na	No	There is no	None	Yes	We assess	Cochrane F	Mixed (Neg
No statema	na	Yes	Reports no	na	Yes	The Cochra	Cochrane F	Mixed (Neg
Public	Drs. Knight	Yes	Includes 1	Evan Wood	Yes	Risk of bias	Cochrane F	Mixed (Neg
No funding	Unfunded v	Yes	Reports no	Declaration	Yes	—RCTs/cR	Cochrane F	Unfavorable
Governmer	This study v	Yes	Reports no	none	Yes	The revise	CONSORT	Mixed (Neg
Public	Funding: D	Yes	Reports no	none	Yes	Study quali	Downs & B	Mixed (Neg
No funding	Nothing de	Yes	Reports no	none	Yes	The quality	Downs and	Unfavorable
No funding	no funding	Yes	Reports no	no competi	Yes		Downs and	Favorable (
Public	Supported	No	There is no	None	Yes	Seventeen	Downs and	Favorable (

1									
2									
3	No funding	This work r	Yes	Reports no	The author:	Yes	We used th	Effective P	Unfavorable
4	Public	E.S. is sup	Yes	Includes 1	E.S. is sup	Yes	Individual r	EPHPP	Mixed (Neg
5	Public	Authors em	Yes	Reports no	No conflict	Yes	Authors ass	GRADE	Mixed (Neg
6	No funding	None	Yes	Reports no	Conflict of	Yes	We determi	Jadad + Cc	Mixed (Neg
7	No statemo	na	Yes	Reports no	On behalf c	Yes	We also me	JADAD Sca	Mixed (Neg
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The evaluation of financial conflicts of interest in addiction medicine systematic reviews and meta-analysis

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Title: The evaluation of financial conflicts of interest in addiction medicine systematic reviews and meta-analysis

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Total words: 35
Tables: 3
Figures: 2

Abstract:

Objective: To quantify conflicts of interest, assess the accuracy of authors self-reporting them, and examine the association between conflicts of interest and favorability of results and discussions in addiction medicine systematic reviews.

Design: A search was performed on MEDLINE (Ovid) from January 2016 to April 25th, 2020 to locate systematic reviews and meta-analyses focused on treatments of addiction disorders using a systematic search strategy. Data were extracted from each systematic review, including conflict of interest statements, authorship characteristics, and the favorability of the results/conclusion sections. A search algorithm was used to identify any undisclosed conflicts of interest on the Open Payments Database (Dollars for Docs), Dollars for Profs, Google Patents/United States Patent and Trade Office, and prior conflict of interest statements in other published works from these authors.

Results: The search identified 127 systematic reviews, representing 665 unique authors. Of the 127 studies, 81 reported no authors with conflicts of interest, 28 with 1 or more conflict, and 18 had no conflict of interest statement. Additional non-disclosed conflicts of interest were found on the Open Payments Database (n=10), Dollars for Profs (n=1), registered patents (n=3), and PubMed searches of other authored publications (20). There were 69 reviews that had at least one author with a conflict of interest. Of the 69 reviews, 14 (20.3%) reported favorable results and 26 (37.7%) reported favorable discussion/conclusions . No statistically significant association was found between systematic reviews with at least one conflicted author and the favorability of results (P = 0.14) or the discussion/conclusion (P = -0.61)

Conclusion: Although multiple undisclosed financial conflicts of interest were found, there was no correlation with the favorability of the results or discussion/conclusions in the addiction medicine systematic reviews.

Keywords: Psychiatry, Addiction Medicine, Conflicts of Interest, Bias, Evidence-based medicine

Article Summary:
- We included systematic reviews and meta-analysis in addiction medicine published between January 2016 to April 25th, 2020
- Articles were initially screened by abstract using Rayyan in a double-blind fashion and then by full-text to ensure they met inclusion criteria. Study characteristics and COI statement information were extracted from each systematic review.
- A step-by-step systematic search algorithm was used to identify undisclosed conflicts of interest through the Open Payments Database, Dollars for Profs, Google Patents/United States Patent and Trade Office, and PubMed for other studies conducted by the authors in our sample. No statistically significant correlation was found between systematic reviews that had at least one author with a disclosed or undisclosed conflict of interest and the favorability of the results and conclusion.
- Financial conflicts of interest is a prominent focus in research currently and continued studies should evaluate how they continue to change or address them in the future.

Introduction

In 2018, 20.3 million people were classified as having substance dependence or abuse[1]. Between 1999 and 2018, more than 700,000 Americans died from overdose [2].The National Institute on Drug Abuse estimates that tobacco, alcohol, and illicit drug misuse results in roughly $740 billion spent on crime, unemployment, and health care[3]Despite the large number of prevention and treatment programs implemented over the last 35 years and the billions of dollars spent to fund them[4], we are now faced with a significant health crisis. The high prevalence of substance abuse, with the increased mortality and morbidity associated with addiction prompts the need for rigorous research to guide treatment plans.[5]

Physicians make treatment decisions using evidence-based clinical practice guidelines; oftentimes, these guidelines include systematic reviews as supporting evidence for treatment recommendations. The American Society of Addiction Medicine's (ASAM) 2020 *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use[6]* used 35 systematic reviews in the updated guideline and provides recommendations for the use of pharmacological treatments including methadone, buprenorphine, and naltrexone. The American Psychiatric Association (APA) also has a recently updated guideline for alcohol use disorder citing 15 systematic reviews used in the rationale for treatment options[7].

Given the influence of systematic reviews on clinical judgment and treatment regimens, they must be well conducted and well reported. Careful attempts should be made to mitigate the effects of bias on systematic review outcomes. Two forms of bias —industry sponsorship and conflicted authors — have both been shown to result in bias affecting the results in numerous publications[8–10].

Further exacerbating this problem of financial bias is the inaccurate reporting of conflicts of interest Andreatos and colleagues[11] found more than 87% of general payments to authors of clinical guidelines were inaccurately reported. A specific analysis of 3 top psychiatry practice guidelines reported that 90% of authors had a financial tie to the drug manufacturer and none of them correctly reported a conflict of interest[12]. Previously published literature has revealed the pervasiveness for conflicted authors in psychiatric and other medical specialty trials with associated positive outcomes.[13–15] With the negative effects that conflicts of interest have on publications outcomes, further research must be done to limit conflicts and increase accurate reporting when present[16].

The Sunshine Act promoted greater transparency ofUS physician disclosures such as honoraria, travel expenses and ownership.[17] The Open Payments Database (Dollars for Docs) contains information regarding the financial relationships between manufacturers of devices/pharmaceuticals andUS based physicians. Researchers have previously used and continue to use Open Payments as a tool for cross-referencing US-based physician authors and their financial disclosure statements.[18–20] Databases such as ProPublica's Dollars for Profs provides a resource for searching the reported disclosures of PhDs who are employed through public universities. Given that bias of competing interest must be accounted for, this study aims to assess the accuracy of disclosure practices among authors of systematic reviews investigating treatments of addiction medicine and to investigate the associations between conflicts of interest and industry funding and the nature of the results and discussions in the systematic reviews.

Methods

Transparency, Reproducibility, and Reporting
We have provided study materials and protocol on Open Science Framework to increase the transparency and reproducibility of our results.[21] While drafting this paper, we referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[22] and Murad and Wang's guidelines for meta-epidemiological studies.[23]

Search strategy
MEDLINE (Ovid) was searched from January 2016 to April 25th, 2020 to locate systematic reviews and meta-analyses focused on treatments of addiction disorders using the search strategy provided in the online protocol.[21] The search results were then uploaded to a systematic review screening platform, Rayyan (https://rayyan.qcri.org/).

Screening
Two investigators (SD and SS) screened abstracts and titles for all search returns in a masked, duplicate manner. Full-text articles were evaluated following title and abstract screening to determine final inclusion. Disagreements were discussed until a consensus was reached. Additional authors were available for third-party arbitration.

Eligibility Criteria
We used the PRISMA-P definition of a systematic review/meta-analysis, which states that a systematic review is "a review of a clearly formulated question that uses systematic and explicit methods to identify, select, critically appraise relevant research, and collect/analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies. Meta-analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies."[24].

Included studies were a systematic review or meta-analysis designed to address interventions for drug, alcohol or tobacco. Furthermore, to qualify for inclusion, systematic reviews must have been published between September of 2016 and the date which the search was conducted (April 25, 2020). We chose the pre-specified date range from September 2016 forward to allow 36 months from the time of the Open Payments Database which appeared online in September 2013. The date range (January 2016 to April 25th, 2020) was selected according to the International Committee of Medical Journal Editors' (ICJME) recommendation that any financial interests be disclosed up to 36 months prior to the time of journal submission.[25] We chose the pre-specified date range to allow 36 months from the time the search of MEDLINE was conducted as the Open Payments Database began publishing data from August 2013.

Only systematic reviews published in English and reviews which synthesize studies of human data were included. The following study types were excluded from our study: observational studies (case-control, cohort, surveys), clinical trials, narrative reviews, systematic reviews not related to (1) drug, alcohol and tobacco addiction prevention, (2) stabilization following excessive use of a substance, (3) relapse prevention or (4) recovery maintenance, duplicates, withdrawn or retracted studies, non-human studies, systematic reviews without abstracts, letters to the editor, and any remaining study which does not meet the inclusion criteria.

Training

All investigators were required to complete online training modules, which provided an overview of the study design, objectives of the study, study materials, and examples of data extraction from systematic reviews. The training was recorded and is available online for reference.[21]

Data extraction

Two authors performed data extraction independently in a masked, duplicate fashion. Data extraction was performed in June/July of 2021 to provide sufficient time for the Open Payments Database or other databases to update information for their prior year. Investigators extracted the following data items from each SR: (1) PubMed identification number and/or DOI; (2) journal name; (3) date of publication; (4) name of author(s); (5) affiliation(s) for the first and last author; (6) author funding source; (7) complete COI statement; (8) whether the SR or meta-analysis addressed risk of bias (RoB); (11) the verbatim RoB statement; (12) whether author(s) were also an author on one or more of the primary studies included in the review (yes/no); (13) total number of self-cited primary studies; (14) primary outcome; and (15) whether narrative results and conclusions favored the treatment or comparison group (e.g., placebo, standard of care, control). We used the term "conclusion" to represent a combination of the discussion and conclusion section of included reviews. Author Funding sources for the systematic review were categorized as follows: industry, government, private non-profit, mixed, other, not funded, or not disclosed. Each possible conflict of interest was reviewed to ensure that it was relevant to the topic being studied. Irrelevant conflicts of interest were not counted for the purpose of this study. Conflicts of interest were all considered equally weighted as the primary endpoint was to see if there was a correlation between authors with any conflict and the favorability of the SR results or discussion/conclusion towards the treatment group.

Favorability of narrative results and conclusions

Narrative results and conclusions were designated as "favorable", "unfavorable", or "mixed/inconclusive". To evaluate the favorability of results and conclusions, we defined a favorable result or conclusion as one where the authors of the systematic review directly stated or implied in the results or conclusion section that the experimental group was determined to be definitively or probably superior to the control group or placebo. An unfavorable result or conclusion was defined as one where the authors of the systematic review directly stated or implied that the experimental group was not superior to the control group or placebo. When appraising the results section, "favorable" was assigned to SRs with only positive results. "Unfavorable" was assigned when negative results were exclusively reported. "Mixed/inconclusive" was assigned to narrative results sections that included both positive and negative results with no clear interpretation of the results. When appraising the conclusion sections, "favorable" was assigned to when authors stated or implied favorability towards the target intervention. "Unfavorable" was assigned when authors stated or implied favorability towards the comparison or control group. When neither "favorable" nor "unfavorable" applied to the conclusion, "mixed/inconclusive" was assigned (i.e., reporting negative population outcome but positive subgroup analysis).

Identification of undisclosed COI

Searches for undisclosed COI were undertaken using the algorithm provided in Figure 1. This stepwise search was based on the methodology provided by Mandrioli et al.,[8] with modifications. These modifications included the incorporation of 3 additional databases — the Open Payments database (Dollars for docs), Dollars for Profs, the United States Patent and Trademark Office (USPTO). Dollars for Profs was included as it catalogs self-reported financial payments received by professors. To ensure consistency between investigators, authors created standardized search strings for PubMed, USPTO Database, and Google Patents using the Python programming language (Python Software Foundation, https://www.python.org/). If we were unable to verify a patent belonged to the author, we considered the search inconclusive and continued our process. In accordance with ICMJE standards of COI disclosure, PubMed searches were limited to 36 months prior to the publication of the original SR to determine if previously published studies included additional COI not disclosed in the SR from our sample. If this search yielded more than 20 publications, each investigator individually assigned random numbers to the resulting publications. The COI statement of the first 20 studies numerically was then examined. Each investigator individually generated random numbers to include a wider search of publications and opportunities for authors to disclose a COI. This process was performed until an undisclosed COI was discovered, at which time the author was then counted as having an undisclosed COI. This stop-procedure is identical to that used by Mandrioli et al.[8]

Risk of bias evaluations
To evaluate the risk of funding bias, we applied the Cochrane Collaboration's criteria for assessment, and the following 4 items from Mandrioli et al[8]: (1) whether explicit and "well defined" criteria that could be replicated by others were used to select studies for inclusion/exclusion; (2) whether an adequate study inclusion method, with two or more assessors selecting studies, was used; (3) whether search strategies were comprehensive; and (4) whether methodological differences that may introduce bias were controlled for. Each item was designated as yes, no, or unclear. We considered the overall RoB to be low if at least 3 of the aforementioned criteria were sufficiently met. Otherwise, the RoB was considered to be high. Authors S.D. and S.S. performed an independent and masked evaluation of risk of bias items. Discrepancies were discussed between investigators until a consensus was reached. D.T. and M.V. were available for third-party adjudication.

Statistical Analysis
Results were quantified using descriptive statistics, and relationships were evaluated by Fisher's exact tests, when possible. Stata 16.1 (StataCorp, LLC, College Station, TX) was used for all analyses. Because of the correlational nature of the research design, a power analysis was not performed.

Patient and Public Involvement
Patients and the public were not involved in the development of the research design or question addressed in this study. This study evaluated systematic reviews, meta-analyses, and the authors of such publications. No patients or health information was used in this study.

Ethics Approval
An institutional review board and ethics review was not required as there were no animal or human subjects involved in this research study.

Results

Sample Characteristics

A total of 1331 manuscripts published between January 2016 and April 25th 2020 were identified using the search string listed in online materials. Of the initial sampling, two researchers reviewed each through rayyan.com and determined that 321 met the inclusion criteria. Of the 321 initially included publications, 194 were excluded after a full-text review. The reasons for exclusion included 62 being outside the date range, 43 not being a systematic review, 27 being a published poster/abstract, 59 did not address the 4 treatment areas of addiction evaluated here, and 3 were inaccessible even after interlibrary loan request. A final number of 127 publications were evaluated for authors with financial conflicts of interest (Figure 1).

The journals with the most publications analyzed include *Addiction* (30*), Drug and Alcohol Dependance* (18), *Addictive Behaviors* (14), *Journal of Substance Abuse Treatment* (14), *and Nicotine & Tobacco Research* (12). The interventions used in each publication includes pharmacological (64), behavioral therapy/psychosocial treatments (53), prevention of addiction (8), and procedures (2).

Conflicts of Interest Statements within Publications

Of the 127 systematic reviews or meta-analyses identified , 28 contained a statement reporting 1 more conflict of interest, 81 reported no authors with conflicts of interest, and 18 provided no conflict of interest statement. Public funding was the most commonly reported with 66 of the 127 publications compared to university (4), public & university (3), and private/industry (2). Furthermore, 33 declined receiving any funding and 19 did not have a statement addressing funding (Table 1). A total of 69 of the systematic reviews were found to have a least one author with a conflict of interest. Of the 127 publications, 104 (81.9%) of those were found to have a high risk of bias including 62 which were found to have a conflict of interest.

Author Specific Conflicts of Interest

Of the 127 systematic reviews analyzed, 655 total authors were identified. The most common countries of origin included the United States (276), United Kingdom (116), Canada (69), and Australia (61). Publications with conflict of interest statements listed 103 of the 655 authors as having a conflict of interest. By searching the Open Payments database, 21 authors had profiles, 15 reported receiving financial payments, and 10 authors receiving funding did not report it as specified by *ICMJE* standards. Additional undeclared conflicts of interest were identified on Dollars for Profs (1), registered patents (3), and PUBMED searches of other authored publications (20) (Table 2).

Favorability of results or discussion/conclusion related to financial conflicts of interest

Of the 127 systematic reviews, a total of 69 (54.3%) had at least one author with a relevant conflict of interest that was initially reported or found through the search algorithm. The systematic reviews with financial conflicts of interests reported favorable results in 14 (20.3%) studies and favorable discussion/conclusions in 26 (37.7%). There was no statistically significant correlation between a systematic review having at least one or more conflict of interest and the

favorability of results (P = 0.138, Fisher's exact) or the favorability of the discussion/conclusion (P = -0.611, Fisher's exact) (Table 3).

Discussion

The primary endpoint of this study was between systematic reviews with one or more authors having a conflict of interest and the nature of the results or conclusions. For this sample of addiction systematic reviews, there was no statistically significant correlation found. Continued research into conflicts of interest and the effects they have on study outcomes is important as multiple publications have found that authors that receive funding from pharmaceutical companies are more favorable with the reporting of results and recommendations than research performed independently[8,26,27].

Multiple authors in the systematic reviews were found to inaccurately report or did not report a financial conflict of interest at all. Of the 655 authors, 105 (16%) had an undisclosed conflict, which represents nearly 1-in-6 authors. We presume that the true number of authors with undisclosed conflicts of interest is underestimated since only US physician researchers have a legal responsibility to list financial support on The Open Payments website. Thus, non-US authors may have undisclosed conflicts that were not findable through our searches. This finding concerns us, as a large and consistent body of evidence indicates that self-disclosure is inaccurate. For example, Wayant et al., reported that approximately one-third of oncologist authors of pivotal cancer therapy trials (i.e., establishing the basis for drug approval) did not disclose financial conflicts with the industry sponsor. We believe that transparency and third party reporting structures are necessary to successfully mitigate this issue. It is therefore critical to think about alternative reporting mechanisms to improve public trust in science and for readers of research studies to be able to critically evaluate the likelihood of financial bias on decision making, results, and discussions.

Another concerning finding is that authors who referenced their own papers in the systematic review were more likely to have an undisclosed conflict of interest. Self-citations increase important research metrics, such as the h-index (for some calculations) and the number of citations received by the author. Thus, there may be possibilities where authors may selectively favor their own studies for inclusion in systematic reviews. There are potentially countless reasons for self-citation that could include increasing one's academic profile or increasing the impact of previous research. We acknowledge that determining which characteristics might contribute to these relationships between undisclosed conflict of interest and self-citations is outside the scope of our current investigation. Additionally, authors of systematic reviews may be experts in their field or perform research on a narrow topic. These authors may be appropriate when performing a systematic review but should be forward about the inclusion of their own research and address any other potential bias that may stem from it. Future research that expands upon this finding is warranted and encouraged.

Although these findings demonstrate no relationship between conflicts of interest and addiction medicine systematic review favorability, it is still important to improve reporting and limit possible opportunities in the future. The author guidelines section of the top 5 psychiatry journals based on Google Scholar metrics was performed. These journals included *Biological Psychiatry, JAMA psychiatry, Molecular Psychiatry, American Journal of Psychiatry,* and *The Lancet Psychiatry* all require an accurate statement for individual authors on a publication. The

requirements for these statements are very specific but there is no mention of verifying the information reported. We recommend that journals implement a screening protocol to search the Open Payments database at the very least for possible undisclosed conflicts of interest. Regarding database selection to uncover undisclosed conflicts, PubMed produced the greatest yield. The Open Payments Database is desirable because the data contained within it are not self-disclosed; however, only healthcare workers are currently listed. Many authors of systematic reviews are not health care workers; instead, they are methodologists, epidemiologists, scientists, research assistants, or students. In these cases, Open Payments will not provide a significant yield. In an effort to include non-physician scientists in our search, we used Dollars for Profs, which was created by ProPublica from NIH COI records. Again, this database is limited to author self-disclosure. It yielded little return and may not be worth considering in future investigations. Likewise, our patent searches generated very few returns. Searching patent databases such as 'Google patents' for discrepancies in disclosure statements has been previously verified as a valid tool for locating undisclosed patents.[28] The use of the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM) for examining consistency in authors' disclosure statements between separate publications has previously been validated as a source for identifying discrepancies.[29].

Strength and limitations
This study was subject to both strengths and limitations. Regarding its strengths, our study was performed in duplicate across screening and data extraction phases by two of the authors who were masked throughout. Performing the study in duplicate limits errors in data extraction and errors in study selection. This process is considered the gold standard methodology of the Cochrane Collaboration[30]. We performed this study according to a previously developed and published protocol, and any deviations to our protocol were described in subsequent protocol updates. Regarding its limitations, we may have not included relevant systematic reviews or our searches may not have retrieved all relevant systematic reviews. Furthermore, there is always the possibility that the authors who performed data extraction exercised some degree of subjectivity, especially related to whether a systematic review conclusion favored the intervention or not. Sample size in our study is also a limitation. International authors with conflicts of interest may be under-reported as there is no legal obligation outside of the United States to report such payments. This under-reporting may alter findings by increasing the number of systematic reviews with conflict authors. Because of the correlational design of this study, our results should not be generalized to other authors or systematic reviews in other fields. Rather, our results should be viewed descriptively. Studies across other specialties are needed so a meta-analysis can be performed to provide a more informed understanding of whether authors with COIs are more likely to report results and conclusions favoring the intervention.

Conclusion:
Our study found that there was no relationship between authors with conflicts of interest and the favorability of the systematic review discussion/conclusion. Although there was no correlation, we did identify 105 authors with undisclosed financial conflicts of interest.

Funding

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Table 1: Characteristics of included systematic reviews and meta-analysis

Characteristic	Form Response	N (%)
Journal in which systematic reviews were published (n= 127)	Addiction	30 (23.6)
	Drug and Alcohol Dependance	18 (14.2)
	Addictive Behaviors	14 (11.0)
	Journal of Substance Abuse Treatment	14 (11.0)
	Nicotine and Tobacco Research	12 (9.4)
	Alcohol and Alcoholism	6 (4.7)
	Other*	33 (26.0)
Conflict of Interest Statement (n=127)	All authors report no COI	81 (63.8)
	No COI statement present	18 (14.1)
	One or more authors report a COI	28 (22.0)
Intervention Type (n= 127)	Pharmacologic	64 (50.4)
	Procedure	2 (1.6)
	Behavioral Therapy/Psychosocial treatments	53 (41.7)
	Prevention	8 (6.3)
Affiliation of First Author (n= 127)	Public Academic Institution	92 (72.4)
	Private Academic Institution	15 (11.8)
	Government	14 (11.0)
	Public academic institution, government	1 (0.8)
	Non-profit institution	4 (3.1)
	Private-for-profit	1 (0.8)

	Public Academic Institution	94 (74.0)
	Private Academic Institution	15 (11.8)
Affiliation of Last Author (n= 127)	Government	13 (10.2)
	Public academic institution, government	1 (0.8)
	Non-profit institution	3 (2.4)
	Private-for-profit	1 (0.8)
	No funding received	33 (26.0)
	No statement listed	19 (15.0)
Author Source of Funding (n= 127)	Private/Industry	2 (1.6)
	Public	66 (52.0)
	University	4 (3.1)
	Public and University	3 (2.4)
Self-citation of primary studies (n=127)	No, did not include self-cited primary studies	109 (85.8)
	Yes, included one or more self-cited primary studies	18 (14.2)

Table 2: Characteristics of systematic review authors (n= 655)

Accuracy of author COI disclosure statement (n= 655)	Reported conflict of interest	103 (81.1)
	Undisclosed FCOI found on Open Payments database	10 (7.9)
	Undisclosed FCOI found on Docs for Profs	1 (0.8)
	Undisclosed FCOI found by patents	3 (2.4)
	Undisclosed FCOI found on PubMed	71 (55.9)
	Additional FCOI besides what is already declared	20 (15.7)
Country of affiliation for authors conducting the systematic review (n= 655)	United States	276 (42.1)
	United Kingdom	116 (17.7)
	Canada	69 (10.5)
	Australia	61 (9.3)
	India	17 (2.6)
	Netherlands	16 (2.4)
	Germany	15 (2.3)
	China	13 (2.0)
	Ireland	11 (1.7)
	Malaysia	11 (1.7)
	Switzerland	9 (1.4)
	France	7 (1.1)
	Belgium	6 (0.9)
	Spain	6 (0.9)
	Other	22 (3.4)

Table 3. Frequency of favorability of results and conclusions if there is a pertinent conflict of interest

Review Outcome	No financial conflict of interest	Financial conflict of interest	Fisher's Exact
Favorability of Results			
Results Favor Treatment Group	20	14	
Results are Mixed/Inconclusive	25	41	
Results Favor Placebo or Control Group	13	14	P = 0.138
Favorability of Discussion/Conclusions			
Discussion Favors Treatment Group	27	26	
Discussion is Mixed/Inconclusive	20	27	
Discussion Favors Placebo or Control Group	11	16	P = 0.822

Figure 1: Search pattern to identify undisclosed financial conflicts of interest

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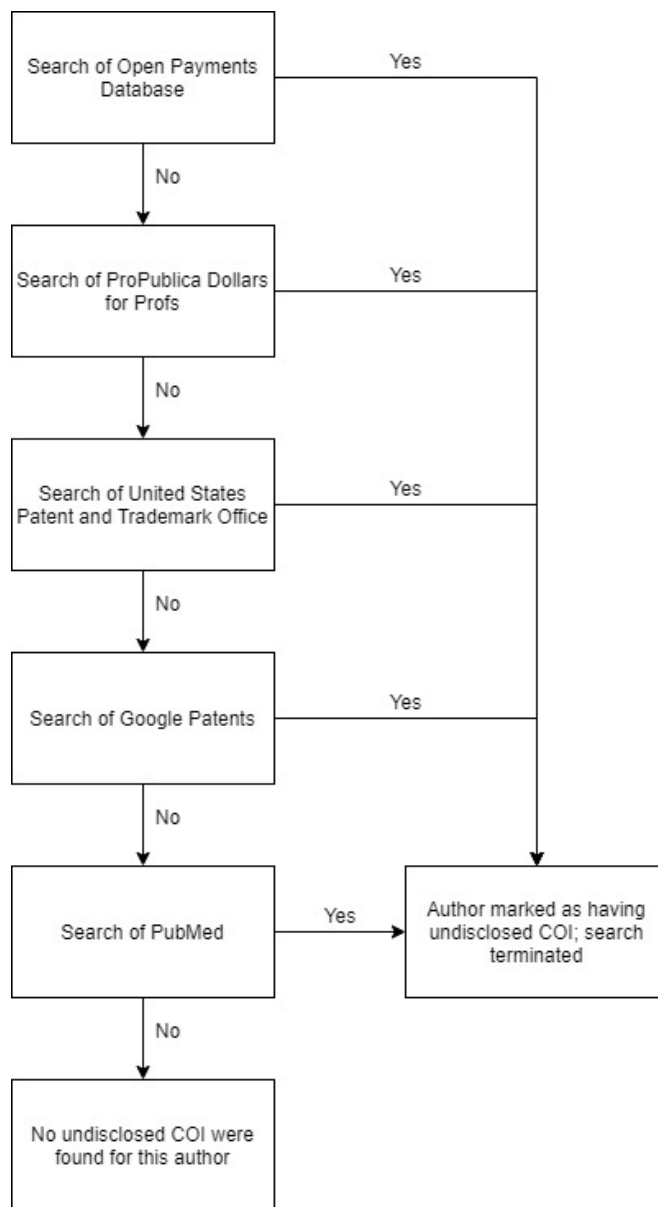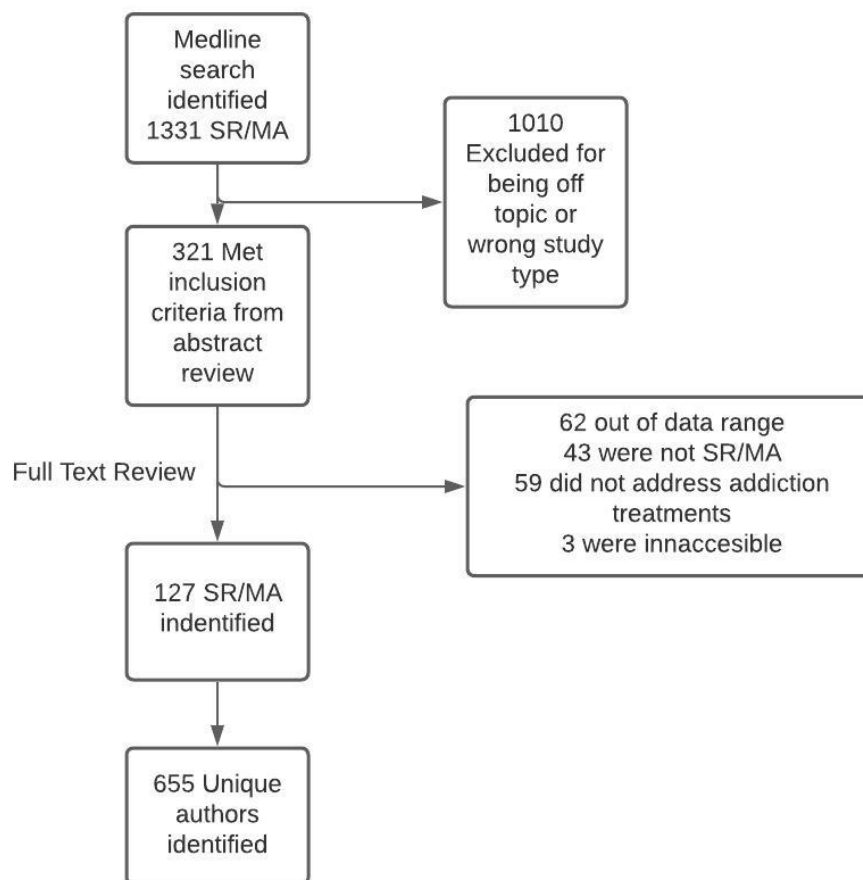Figure 2: Stepwise progression of search strategy to identify SR/MA and authors in addiction medicine.

Figure 1: Search pattern to identify undisclosed financial conflicts of interest

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Figure 2: Stepwise progression of search strategy to identify SR/MA studies and authors in addiction medicine.

139x134mm (160 x 160 DPI)

BMJ Open

Correlation analysis of financial conflicts of interest and favorability of results or conclusions in addiction medicine systematic reviews and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054325.R2
Article Type:	Original research
Date Submitted by the Author:	12-May-2022
Complete List of Authors:	Vassar, Matthew; Oklahoma State University Center for Health Sciences, Psychiatry Shepard, Samuel; Oklahoma State University Center for Health Sciences, Medical Student Research Demla, Simran; Oklahoma State University Center for Health Sciences, Medical Student research Tritz, Daniel; Oklahoma State University Medical Center
\Primary Subject Heading\:	Addiction
Secondary Subject Heading:	Addiction, Evidence based practice
Keywords:	PSYCHIATRY, STATISTICS & RESEARCH METHODS, QUALITATIVE RESEARCH, Substance misuse < PSYCHIATRY

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Title: Correlation analysis of financial conflicts of interest and favorability of results or conclusions in addiction medicine systematic reviews and meta-analysis

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Total words: 3649
Tables: 3
Figures: 2

Abstract:

Objective: To quantify conflicts of interest, assess the accuracy of authors self-reporting them, and examine the association between conflicts of interest and favorability of results and discussions in addiction medicine systematic reviews.

Design: A search was performed on MEDLINE (Ovid) from January 2016 to April 25th, 2020 to locate systematic reviews and meta-analyses focused on treatments of addiction disorders using a systematic search strategy. Data were extracted from each systematic review, including conflict of interest statements, authorship characteristics, and the favorability of the results/conclusion sections. A search algorithm was used to identify any undisclosed conflicts of interest on the Open Payments Database (Dollars for Docs), Dollars for Profs, Google Patents/United States Patent and Trade Office, and prior conflict of interest statements in other published works from these authors.

Results: The search identified 127 systematic reviews, representing 665 unique authors. Of the 127 studies, 81 reported no authors with conflicts of interest, 28 with 1 or more conflict, and 18 had no conflict of interest statement. Additional non-disclosed conflicts of interest were found for 34 authors. There were 69 reviews that had at least one author with a conflict of interest. Of the 69 reviews, 14 (20.3%) reported favorable results and 26 (37.7%) reported favorable discussion/conclusions with no statistically significant association. A sub-analysis was performed on publications with only United States (US) authors (51) with 35 (68.9%) having at least 1 conflict of interest. US authored studies that had a conflict of interest favored the results (P = <0.001) and discussion/conclusion (P = 0.018) more often.

Conclusion: Although multiple undisclosed financial conflicts of interest were found, there was no correlation with the favorability of the results or discussion/conclusions across all addiction medicine systematic reviews. Further research needs to be done on US-based publications and encourage disclosure systems worldwide to provide more accurate reporting.

Keywords: Psychiatry, Addiction Medicine, Conflicts of Interest, Bias, Evidence-based medicine

Article Summary:

- We included systematic reviews and meta-analysis in addiction medicine published between January 2016 to April 25th, 2020
- Articles were initially screened by abstract using Rayyan in a double-blind fashion and then by full-text to ensure they met inclusion criteria. Study characteristics and COI statement information were extracted from each systematic review.
- A step-by-step systematic search algorithm was used to identify undisclosed conflicts of interest through the Open Payments Database, Dollars for Profs, Google Patents/United States Patent and Trade Office, and PubMed for other studies conducted by the authors in our sample. No statistically significant correlation was found between systematic reviews that had at least one author with a disclosed or undisclosed conflict of interest and the favorability of the results and conclusion.
- Financial conflicts of interest is a prominent focus in research currently and continued studies should evaluate how they continue to change or address them in the future.

Introduction

In 2018, 20.3 million people were classified as having substance dependence or abuse[1]. Between 1999 and 2018, more than 700,000 Americans died from overdose [2].The National Institute on Drug Abuse estimates that tobacco, alcohol, and illicit drug misuse results in roughly $740 billion spent on crime, unemployment, and health care[3]Despite the large number of prevention and treatment programs implemented over the last 35 years and the billions of dollars spent to fund them[4], we are now faced with a significant health crisis. The high prevalence of substance abuse, with the increased mortality and morbidity associated with addiction prompts the need for rigorous research to guide treatment plans.[5]

Physicians make treatment decisions using evidence-based clinical practice guidelines; oftentimes, these guidelines include systematic reviews as supporting evidence for treatment recommendations. The American Society of Addiction Medicine's (ASAM) 2020 *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use[6]* used 35 systematic reviews in the updated guideline and provides recommendations for the use of pharmacological treatments including methadone, buprenorphine, and naltrexone. The American Psychiatric Association (APA) also has a recently updated guideline for alcohol use disorder citing 15 systematic reviews used in the rationale for treatment options[7].

Given the influence of systematic reviews on clinical judgment and treatment regimens, they must be well conducted and well reported. Careful attempts should be made to mitigate the effects of bias on systematic review outcomes. Two forms of bias —industry sponsorship and conflicted authors — have both been shown to result in bias affecting the results in numerous publications[8–10].

Further exacerbating this problem of financial bias is the inaccurate reporting of conflicts of interest Andreatos and colleagues[11] found more than 87% of general payments to authors of clinical guidelines were inaccurately reported. A specific analysis of 3 top psychiatry practice guidelines reported that 90% of authors had a financial tie to the drug manufacturer and none of them correctly reported a conflict of interest[12]. Previously published literature has revealed the pervasiveness for conflicted authors in psychiatric and other medical specialty trials with associated positive outcomes.[13–15] With the negative effects that conflicts of interest have on publications outcomes, further research must be done to limit conflicts and increase accurate reporting when present[16].

The Sunshine Act promoted greater transparency ofUS physician disclosures such as honoraria, travel expenses and ownership.[17] The Open Payments Database (Dollars for Docs) contains information regarding the financial relationships between manufacturers of devices/pharmaceuticals andUS based physicians. Researchers have previously used and continue to use Open Payments as a tool for cross-referencing US-based physician authors and their financial disclosure statements.[18–20] Databases such as ProPublica's Dollars for Profs provides a resource for searching the reported disclosures of PhDs who are employed through public universities. Given that bias of competing interest must be accounted for, this study aims to assess the accuracy of disclosure practices among authors of systematic reviews investigating treatments of addiction medicine and to investigate the associations between conflicts of interest and industry funding and the nature of the results and discussions in the systematic reviews.

Methods

Transparency, Reproducibility, and Reporting
We have provided study materials and protocol on Open Science Framework to increase the transparency and reproducibility of our results.[21] While drafting this paper, we referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[22] and Murad and Wang's guidelines for meta-epidemiological studies.[23]

Search strategy
MEDLINE (Ovid) was searched from January 2016 to April 25th, 2020 to locate systematic reviews and meta-analyses focused on treatments of addiction disorders using the search strategy provided in the online protocol.[21] The search results were then uploaded to a systematic review screening platform, Rayyan (https://rayyan.qcri.org/).

Screening
Two investigators (SD and SS) screened abstracts and titles for all search returns in a masked, duplicate manner. Full-text articles were evaluated following title and abstract screening to determine final inclusion. Disagreements were discussed until a consensus was reached. Additional authors were available for third-party arbitration.

Eligibility Criteria
We used the PRISMA-P definition of a systematic review/meta-analysis, which states that a systematic review is "a review of a clearly formulated question that uses systematic and explicit methods to identify, select, critically appraise relevant research, and collect/analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies. Meta-analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies."[24].

Included studies were a systematic review or meta-analysis designed to address interventions for drug, alcohol or tobacco. Furthermore, to qualify for inclusion, systematic reviews must have been published between September of 2016 and the date which the search was conducted (April 25, 2020). We chose the pre-specified date range from September 2016 forward to allow 36 months from the time of the Open Payments Database which appeared online in September 2013. The date range (January 2016 to April 25th, 2020) was selected according to the International Committee of Medical Journal Editors' (ICJME) recommendation that any financial interests be disclosed up to 36 months prior to the time of journal submission.[25] We chose the pre-specified date range to allow 36 months from the time the search of MEDLINE was conducted as the Open Payments Database began publishing data from August 2013.

Only systematic reviews published in English and reviews which synthesize studies of human data were included. The following study types were excluded from our study: observational studies (case-control, cohort, surveys), clinical trials, narrative reviews, systematic reviews not related to (1) drug, alcohol and tobacco addiction prevention, (2) stabilization following excessive use of a substance, (3) relapse prevention or (4) recovery maintenance, duplicates, withdrawn or retracted studies, non-human studies, systematic reviews without abstracts, letters to the editor, and any remaining study which does not meet the inclusion criteria.

Training

All investigators were required to complete online training modules, which provided an overview of the study design, objectives of the study, study materials, and examples of data extraction from systematic reviews. The training was recorded and is available online for reference.[21]

Data extraction

Two authors performed data extraction independently in a masked, duplicate fashion. Data extraction was performed in June/July of 2021 to provide sufficient time for the Open Payments Database or other databases to update information for their prior year. Investigators extracted the following data items from each SR: (1) PubMed identification number and/or DOI; (2) journal name; (3) date of publication; (4) name of author(s); (5) affiliation(s) for the first and last author; (6) author funding source; (7) complete COI statement; (8) whether the SR or meta-analysis addressed risk of bias (RoB); (11) the verbatim RoB statement; (12) whether author(s) were also an author on one or more of the primary studies included in the review (yes/no); (13) total number of self-cited primary studies; (14) primary outcome; and (15) whether narrative results and conclusions favored the treatment or comparison group (e.g., placebo, standard of care, control). We used the term "conclusion" to represent a combination of the discussion and conclusion section of included reviews. Author Funding sources for the systematic review were categorized as follows: industry, government, private non-profit, mixed, other, not funded, or not disclosed. Each possible conflict of interest was reviewed to ensure that it was relevant to the topic being studied. Irrelevant conflicts of interest were not counted for the purpose of this study. Conflicts of interest were all considered equally weighted as the primary endpoint was to see if there was a correlation between authors with any conflict and the favorability of the SR results or discussion/conclusion towards the treatment group.

Favorability of narrative results and conclusions

Narrative results and conclusions were designated as "favorable", "unfavorable", or "mixed/inconclusive". To evaluate the favorability of results and conclusions, we defined a favorable result or conclusion as one where the authors of the systematic review directly stated or implied in the results or conclusion section that the experimental group was determined to be definitively or probably superior to the control group or placebo. An unfavorable result or conclusion was defined as one where the authors of the systematic review directly stated or implied that the experimental group was not superior to the control group or placebo. When appraising the results section, "favorable" was assigned to SRs with only positive results. "Unfavorable" was assigned when negative results were exclusively reported. "Mixed/inconclusive" was assigned to narrative results sections that included both positive and negative results with no clear interpretation of the results. When appraising the conclusion sections, "favorable" was assigned to when authors stated or implied favorability towards the target intervention. "Unfavorable" was assigned when authors stated or implied favorability towards the comparison or control group. When neither "favorable" nor "unfavorable" applied to the conclusion, "mixed/inconclusive" was assigned (i.e., reporting negative population outcome but positive subgroup analysis).

Identification of undisclosed COI

Searches for undisclosed COI were undertaken using the algorithm provided in Figure 1. This stepwise search was based on the methodology provided by Mandrioli et al.,[8] with modifications. These modifications included the incorporation of 3 additional databases — the Open Payments database (Dollars for docs), Dollars for Profs, the United States Patent and Trademark Office (USPTO). Dollars for Profs was included as it catalogs self-reported financial payments received by professors. To ensure consistency between investigators, authors created standardized search strings for PubMed, USPTO Database, and Google Patents using the Python programming language (Python Software Foundation, https://www.python.org/). If we were unable to verify a patent belonged to the author, we considered the search inconclusive and continued our process. In accordance with ICMJE standards of COI disclosure, PubMed searches were limited to 36 months prior to the publication of the original SR to determine if previously published studies included additional COI not disclosed in the SR from our sample. If this search yielded more than 20 publications, each investigator individually assigned random numbers to the resulting publications. The COI statement of the first 20 studies numerically was then examined. Each investigator individually generated random numbers to include a wider search of publications and opportunities for authors to disclose a COI. This process was performed until an undisclosed COI was discovered, at which time the author was then counted as having an undisclosed COI. This stop-procedure is identical to that used by Mandrioli et al.[8]

Risk of bias evaluations
To evaluate the risk of funding bias, we applied the Cochrane Collaboration's criteria for assessment, and the following 4 items from Mandrioli et al[8]: (1) whether explicit and "well defined" criteria that could be replicated by others were used to select studies for inclusion/exclusion; (2) whether an adequate study inclusion method, with two or more assessors selecting studies, was used; (3) whether search strategies were comprehensive; and (4) whether methodological differences that may introduce bias were controlled for. Each item was designated as yes, no, or unclear. We considered the overall RoB to be low if at least 3 of the aforementioned criteria were sufficiently met. Otherwise, the RoB was considered to be high. Authors S.D. and S.S. performed an independent and masked evaluation of risk of bias items. Discrepancies were discussed between investigators until a consensus was reached. D.T. and M.V. were available for third-party adjudication.

Statistical Analysis
Results were quantified using descriptive statistics, and relationships were evaluated by Fisher's exact tests, when possible. Stata 16.1 (StataCorp, LLC, College Station, TX) was used for all analyses. Because of the correlational nature of the research design, a power analysis was not performed.

Patient and Public Involvement
Patients and the public were not involved in the development of the research design or question addressed in this study. This study evaluated systematic reviews, meta-analyses, and the authors of such publications. No patients or health information was used in this study.

Ethics Approval
An institutional review board and ethics review were not required as there were no animal or human subjects involved in this research study.

Results

Sample Characteristics

A total of 1331 manuscripts published between January 2016 and April 25th 2020 were identified using the search string listed in online materials. Of the initial sampling, two researchers reviewed each through rayyan.com and determined that 321 met the inclusion criteria. Of the 321 initially included publications, 194 were excluded after a full-text review. The reasons for exclusion included 62 being outside the date range, 43 not being a systematic review, 27 being a published poster/abstract, 59 did not address the 4 treatment areas of addiction evaluated here, and 3 were inaccessible even after interlibrary loan request. A final number of 127 publications were evaluated for authors with financial conflicts of interest (Figure 2).

The journals with the most publications analyzed include *Addiction* (30*), Drug and Alcohol Dependance* (18), *Addictive Behaviors* (14), *Journal of Substance Abuse Treatment* (14), *and Nicotine & Tobacco Research* (12). The interventions used in each publication includes pharmacological (64), behavioral therapy/psychosocial treatments (53), prevention of addiction (8), and procedures (2).

Conflicts of Interest Statements within Publications

Of the 127 systematic reviews or meta-analyses identified , 28 contained a statement reporting 1 more conflict of interest, 81 reported no authors with conflicts of interest, and 18 provided no conflict of interest statement. Public funding was the most commonly reported with 66 of the 127 publications compared to university (4), public & university (3), and private/industry (2). Furthermore, 33 declined receiving any funding and 19 did not have a statement addressing funding (Table 1). A total of 69 of the systematic reviews were found to have a least one author with a conflict of interest. Of the 127 publications, 104 (81.9%) of those were found to have a high risk of bias including 62 which were found to have a conflict of interest.

Author Specific Conflicts of Interest

Of the 127 systematic reviews analyzed, 655 total authors were identified. The most common countries of origin included the United States (276), United Kingdom (116), Canada (69), and Australia (61). Publications with conflict of interest statements listed 103 of the 655 authors as having a conflict of interest. By searching the Open Payments database, 21 authors had profiles, 15 reported receiving financial payments, and 10 authors receiving funding did not report it as specified by *ICMJE* standards. Additional undeclared conflicts of interest were identified on Dollars for Profs (1), registered patents (3), and PUBMED searches of other authored publications (20) (Table 2).

Favorability of results or discussion/conclusion related to financial conflicts of interest

Of the 127 systematic reviews, a total of 69 (54.3%) had at least one author with a relevant conflict of interest that was initially reported or found through the search algorithm. The systematic reviews with financial conflicts of interests reported favorable results in 14 (20.3%) studies and favorable discussion/conclusions in 26 (37.7%). There was no statistically significant correlation between a systematic review having at least one or more conflicts of interest and the

favorability of results (P = 0.138, Fisher's exact) or the favorability of the discussion/conclusion (P = -0.611, Fisher's exact) (Table 3).

A sub-analysis was performed on the total number of conflicted authors per publication and the favorability of results (P = 0.50) and discussion/conclusion (P = 0.77). An additional sub-analysis was performed on publications with only United States (US) authors (51) with 35 (68.9%) having at least 1 conflict of interest. US authored studies that had a conflict of interest favored the results (P = <0.001) and discussion/conclusion (P = 0.018) more often.

Discussion

The primary endpoint of this study was between systematic reviews with one or more authors having a conflict of interest and the nature of the results or conclusions. For this complete sample of addiction systematic reviews, there was no statistically significant correlation found. A sub-analysis was performed on publications with only US authors. The analysis found a positive correlation between studies with at least one conflicted author showing favorability towards results and discussion/conclusions.Continued research into conflicts of interest and the effects they have on study outcomes is important as multiple publications have found that authors that receive funding from pharmaceutical companies are more favorable with the reporting of results and recommendations than research performed independently[8,26,27].

Multiple authors in the systematic reviews were found to inaccurately report or did not report a financial conflict of interest at all. Of the 655 authors, 105 (16%) had an undisclosed conflict, which represents nearly 1-in-6 authors. We presume that the true number of authors with undisclosed conflicts of interest is underestimated since only US physician-researchers have a legal responsibility to list financial support on The Open Payments website. Thus, non-US authors may have undisclosed conflicts that were not findable through our searches. This finding concerns us, as a large and consistent body of evidence indicates that self-disclosure is inaccurate. For example, Wayant et al., reported that approximately one-third of oncologist authors of pivotal cancer therapy trials (i.e., establishing the basis for drug approval) did not disclose financial conflicts with the industry sponsor. We believe that transparency and third-party reporting structures are necessary to successfully mitigate this issue. It is therefore critical to think about alternative reporting mechanisms to improve public trust in science and for readers of research studies to be able to critically evaluate the likelihood of financial bias on decision making, results, and discussions.

Another concerning finding is that authors who referenced their own papers in the systematic review were more likely to have an undisclosed conflict of interest. Self-citations increase important research metrics, such as the h-index (for some calculations) and the number of citations received by the author. Thus, there may be possibilities where authors may selectively favor their own studies for inclusion in systematic reviews. There are potentially countless reasons for self-citation that could include increasing one's academic profile or increasing the impact of previous research. We acknowledge that determining which characteristics might contribute to these relationships between undisclosed conflict of interest and self-citations is outside the scope of our current investigation. Additionally, authors of systematic reviews may be experts in their field or perform research on a narrow topic. These authors may be appropriate when performing a systematic review but should be forward about the inclusion of their own

research and address any other potential bias that may stem from it. Future research that expands upon this finding is warranted and encouraged.

It is important to improve reporting and limit possible opportunities in the future. The author guidelines section of the top 5 psychiatry journals based on Google Scholar metrics was performed. These journals included *Biological Psychiatry, JAMA psychiatry, Molecular Psychiatry, American Journal of Psychiatry,* and *The Lancet Psychiatry* all require an accurate statement for individual authors on a publication. The requirements for these statements are very specific but there is no mention of verifying the information reported. We recommend that journals implement a screening protocol to search the Open Payments database at the very least for possible undisclosed conflicts of interest. Regarding database selection to uncover undisclosed conflicts, PubMed produced the greatest yield. The Open Payments Database is desirable because the data contained within it are not self-disclosed; however, only healthcare workers are currently listed. Many authors of systematic reviews are not health care workers; instead, they are methodologists, epidemiologists, scientists, research assistants, or students. In these cases, Open Payments will not provide a significant yield. In an effort to include non-physician scientists in our search, we used Dollars for Profs, which was created by ProPublica from NIH COI records. Again, this database is limited to author self-disclosure. It yielded little return and may not be worth considering in future investigations. Likewise, our patent searches generated very few returns. Searching patent databases such as 'Google patents' for discrepancies in disclosure statements has been previously verified as a valid tool for locating undisclosed patents.[28] The use of the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM) for examining consistency in authors' disclosure statements between separate publications has previously been validated as a source for identifying discrepancies.[29].

Strength and limitations
This study was subject to both strengths and limitations. Regarding its strengths, our study was performed in duplicate across screening and data extraction phases by two of the authors who were masked throughout. Performing the study in duplicate limits errors in data extraction and errors in study selection. This process is considered the gold standard methodology of the Cochrane Collaboration[30]. We performed this study according to a previously developed and published protocol, and any deviations to our protocol were described in subsequent protocol updates. Regarding its limitations, we may have not included relevant systematic reviews or our searches may not have retrieved all relevant systematic reviews. Furthermore, there is always the possibility that the authors who performed data extraction exercised some degree of subjectivity, especially related to whether a systematic review conclusion favored the intervention or not. Sample size in our study is also a limitation. International authors with conflicts of interest may be under-reported as there is no legal obligation outside of the United States to report such payments. This under-reporting may alter findings by increasing the number of systematic reviews with conflict authors. The correlation found for strictly US-based authors is difficult to correlate if it's because US authors are more conflicted due to the lack of international reporting. Because of the correlational design of this study, our results should not be generalized to other authors or systematic reviews in other fields. Rather, our results should be viewed descriptively. Studies across other specialties are needed so a meta-analysis can be performed to provide a

more informed understanding of whether authors with COIs are more likely to report results and conclusions favoring the intervention.

Conclusion:
Our study found that there was no relationship between authors with conflicts of interest and the favorability of the systematic review discussion/conclusion.A sub-analysis of authors from the United States found that conflicted publications were more likely to favor the treatment group in results and discussions. We did identify 105 authors with undisclosed financial conflicts of interest.

Data statement
The data used in this study is available at a supplementary file.

Authorship Contributions:
MV: Conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, software, supervision, validation, roles/writing - original draft.
SS: Data Curation, formal analysis, investigation, project administration, validation, visualization, and roles/writing - original draft
SD: Data Curation, formal analysis, investigation, project administration, validation, visualization, and roles/writing - original draft
DT: Conceptualization, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, roles/writing - original draft

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Table 1: Characteristics of included systematic reviews and meta-analysis

Characteristic	Form Response	N (%)
Journal in which systematic reviews were published (n= 127)	Addiction	30 (23.6)
	Drug and Alcohol Dependance	18 (14.2)
	Addictive Behaviors	14 (11.0)
	Journal of Substance Abuse Treatment	14 (11.0)
	Nicotine and Tobacco Research	12 (9.4)
	Alcohol and Alcoholism	6 (4.7)
	Other*	33 (26.0)
Conflict of Interest Statement (n=127)	All authors report no COI	81 (63.8)
	No COI statement present	18 (14.1)
	One or more authors report a COI	28 (22.0)
Intervention Type (n= 127)	Pharmacologic	64 (50.4)
	Procedure	2 (1.6)
	Behavioral Therapy/Psychosocial treatments	53 (41.7)
	Prevention	8 (6.3)
Affiliation of First Author (n= 127)	Public Academic Institution	92 (72.4)
	Private Academic Institution	15 (11.8)
	Government	14 (11.0)
	Public academic institution, government	1 (0.8)
	Non-profit institution	4 (3.1)
	Private-for-profit	1 (0.8)

Affiliation of Last Author (n= 127)	Public Academic Institution	94 (74.0)
	Private Academic Institution	15 (11.8)
	Government	13 (10.2)
	Public academic institution, government	1 (0.8)
	Non-profit institution	3 (2.4)
	Private-for-profit	1 (0.8)
Author Source of Funding (n= 127)	No funding received	33 (26.0)
	No statement listed	19 (15.0)
	Private/Industry	2 (1.6)
	Public	66 (52.0)
	University	4 (3.1)
	Public and University	3 (2.4)
Self-citation of primary studies (n=127)	No, did not include self-cited primary studies	109 (85.8)
	Yes, included one or more self-cited primary studies	18 (14.2)

Table 2: Characteristics of systematic review authors (n= 655)

Accuracy of author COI disclosure statement (n= 655)	Reported conflict of interest	103 (81.1)
	Undisclosed FCOI found on Open Payments database	10 (7.9)
	Undisclosed FCOI found on Docs for Profs	1 (0.8)
	Undisclosed FCOI found by patents	3 (2.4)
	Undisclosed FCOI found on PubMed	71 (55.9)
	Additional FCOI besides what is already declared	20 (15.7)
Country of affiliation for authors conducting the systematic review (n= 655)	United States	276 (42.1)
	United Kingdom	116 (17.7)
	Canada	69 (10.5)
	Australia	61 (9.3)
	India	17 (2.6)
	Netherlands	16 (2.4)
	Germany	15 (2.3)
	China	13 (2.0)
	Ireland	11 (1.7)
	Malaysia	11 (1.7)
	Switzerland	9 (1.4)
	France	7 (1.1)
	Belgium	6 (0.9)
	Spain	6 (0.9)
	Other	22 (3.4)

Table 3. Frequency of favorability of results and conclusions if there is a pertinent conflict of interest

Review Outcome	No financial conflict of interest	Financial conflict of interest	Fisher's Exact
Favorability of Results			
Results Favor Treatment Group	20	14	
Results are Mixed/Inconclusive	25	41	
Results Favor Placebo or Control Group	13	14	P = 0.138
Favorability of Discussion/Conclusions			
Discussion Favors Treatment Group	27	26	
Discussion is Mixed/Inconclusive	20	27	
Discussion Favors Placebo or Control Group	11	16	P = 0.822

Figure 1: Search pattern to identify undisclosed financial conflicts of interest

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Figure 2: Stepwise progression of search strategy to identify SR/MA and authors in addiction medicine.
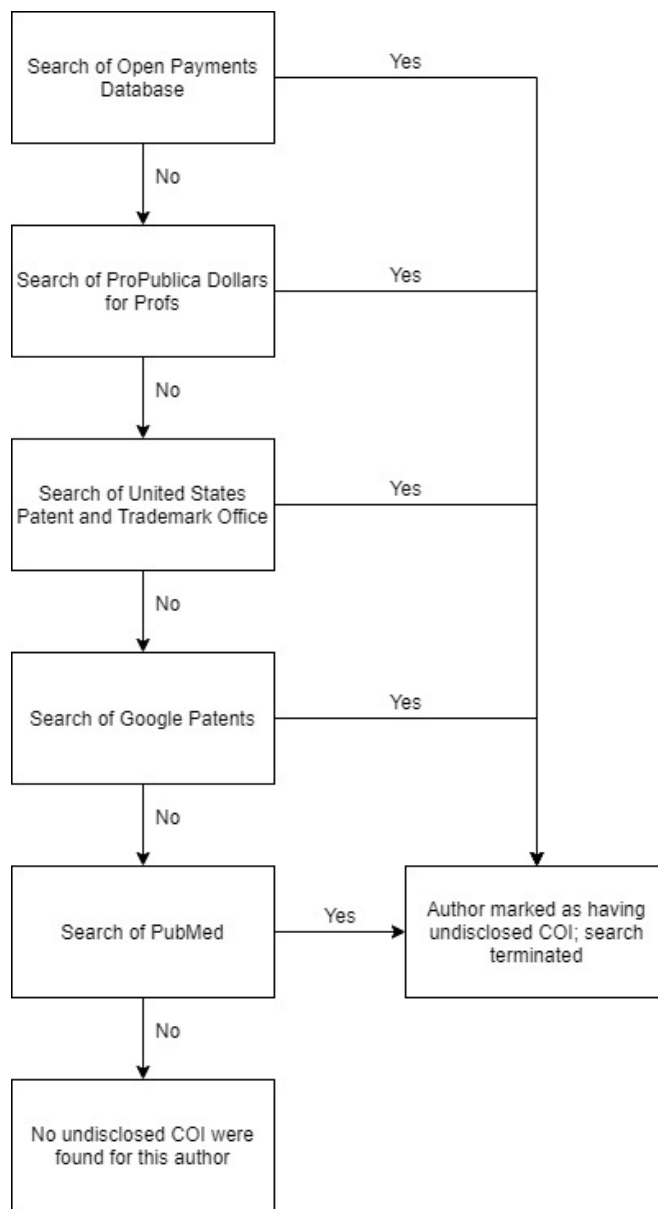
Figure 1: Search pattern to identify undisclosed financial conflicts of interest

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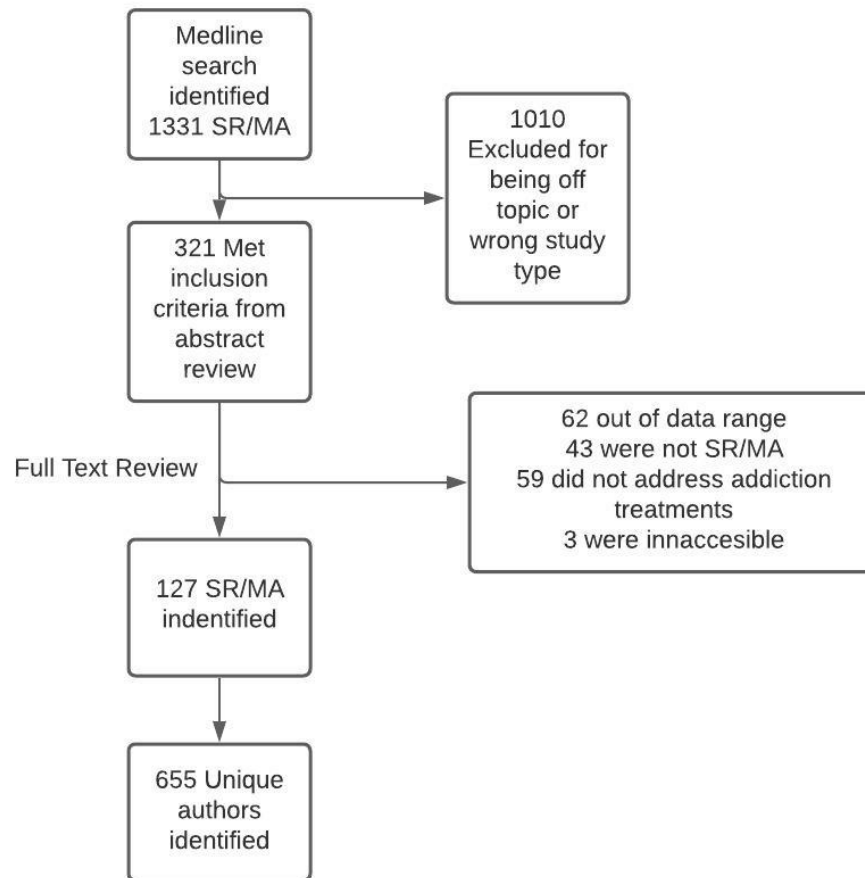41
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Medline search identified 1331 SR/MA

1010 Excluded for being off topic or wrong study type

321 Met inclusion criteria from abstract review

Full Text Review

62 out of data range
43 were not SR/MA
59 did not address addiction treatments
3 were innaccesible

127 SR/MA indentified

655 Unique authors identified

Figure 2: Stepwise progression of search strategy to identify SR/MA studies and authors in addiction medicine.

139x134mm (160 x 160 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	NA
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3,L11
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P3,L43
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P5,L21
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P5,L9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P5,L9
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P5,L15
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P6,L8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P6,L11
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	NA
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P6,L13
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P7,L34
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P7,34
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P9,4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P8,L4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P8,L6
Study characteristics	17	Cite each included study and present its characteristics.	NA
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P9,L11
	23b	Discuss any limitations of the evidence included in the review.	P10,L34
	23c	Discuss any limitations of the review processes used.	P10,L34
	23d	Discuss implications of the results for practice, policy, and future research.	P10,L4
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P11,L12
Competing interests	26	Declare any competing interests of review authors.	P11,L16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P11,L21

PRISMA 2020 Checklist

10.1136/bmj.n71

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