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High prevalence of spin was found in pharmacovigilance studies using disproportionality analyses to detect safety signals: a meta-epidemiological study

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Declaration of interest

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Abstract

Objective

To systematically review and appraise misinterpretation of pharmacovigilance disproportionality analysis results in published studies.

Study Design and Setting

We randomly selected 100 studies that performed disproportionality analyses and indexed in Medline identified during a systematic literature search. Titles, abstracts and main texts (results, discussion and conclusion) were evaluated for spin independently by 2 reviewers. Spin in pharmacovigilance studies was classified according to 3 main categories: inappropriate interpretation, inappropriate extrapolations and misleading reporting.

Results

Of the 100 studies evaluated, we found that 63%, 56% and 51% had at least one type of spin in their abstract, main text or conclusion respectively, and 40% used causal language to interpret their results in the abstract or conclusion. Spin in titles and results were exclusively represented by inappropriate interpretations of findings (12% and 21% respectively), with terms such as “risk of” or “risks associated with” or results erroneously presented as regular Odds Ratios. Spin in discussion sections mostly concerned inappropriate interpretations (38%) and misleading reporting (12%). Misleading reporting, notably failing to acknowledge the limitations of disproportionality analyses, was the most frequent type of spin in abstracts (55%) and conclusion sections (37%).

Conclusion

We found that spin is frequent in publications of pharmacovigilance disproportionality analyses, notably in abstracts. This consisted notably in an over-interpretation of the results suggesting a proven causative link between a drug use and the risk of an event.

Key words: pharmacovigilance, disproportionality analyses, signal detection, spin, reporting

Running title: Spin in pharmacovigilance disproportionality analyses

Word count: 2255

What is new?

- key findings
 - We found a high prevalence of spin in publications of pharmacovigilance disproportionality analyses
 - Over-interpretation of the results suggesting a proven causative link between a drug and adverse events was the most frequent type of spin
- what this adds to what is known
 - Spin in interpretation of pharmacovigilance studies is frequent and may lead to reader's misinterpreting results and unjustified beliefs on the levels of evidence underlying links between drugs and adverse events.
- what is the implication/what should change now
 - Efforts to reduce the prevalence of spin in pharmacovigilance studies are needed
 - The development of reporting guideline may help to reduce spin in pharmacovigilance disproportionality analyses.

1. INTRODUCTION

Disproportionality analyses are hypothesis-generating methods that aim to detect safety signals for medicinal products (i.e. putative links between drugs and adverse drug reactions) from databases containing adverse events that have been spontaneously reported mainly by healthcare professionals or patients [1]. Such methods quantify the degree to which a drug–event pair occurs “disproportionally” compared to what would be expected if there were no association between the drug and the event [2]. That is, they answer the question: “does the number of observed cases exceed the number of expected cases?” [3]. Yet, the actual number of patients exposed to a given drug is unknown and therefore, disproportionality analyses do not provide risk quantification and, taken alone, do not allow any causal inference to be established [4]. However, recent reports have pointed that claiming a causal link from the results of disproportionality analyses might not be an uncommon practice [3,5].

Distortion of study findings, also known as “spin”, were posited in the late 90’s and the first systematic surveys of such practices were published in 2010 about the interpretation of randomized controlled trials with statistically nonsignificant results for their primary outcomes. [6,7] Since that time, the concept of spin has been expanded to all reporting practices that distort the interpretation of results and enhance study findings more than the results justify.[8] Such practices have been identified and quantified in many scientific fields but, to date, no study has assessed these practices in pharmacovigilance studies.[9]

In this context, we aimed at performing a systematic appraisal of misinterpretation of published pharmacovigilance disproportionality analysis results. The objectives of this survey are to 1) identify the nature and estimate the prevalence of spin in titles, abstracts and main texts, and 2) explore the correlation between spin and several characteristics of these studies.

2. MATERIALS AND METHODS

The protocol of our study was preregistered on the Open Science Framework. [10] This study was conducted in parallel with another project evaluating the methods and the reporting characteristics of disproportionality analyses, described elsewhere. [11]

2.1. Development of a classification of spin

Many types of spin have been described. However, based on a systematic review of studies of spin, and in particular a study of spin in non-randomized trials, we classified spin in pharmacovigilance studies into 3 main categories [12,13]:

(a) inappropriate interpretation: use of causal language, including the use of statements that suggested the adverse event was causally linked to the drug (e.g. “*increased risk of an ADR*”, “*increase the incidence of*”) or a tone inferring a strong result (e.g., “*this study shows that*” or “*the results demonstrate*”) etc.

(b) inappropriate extrapolation: while disproportionality signals should be hypothesis-generating methods, spin may appear through assertions about drug safety profiles (e.g. one drug being better or worse than another; claiming the treatment is safe; or giving recommendations for clinical practice; etc).

(c) misleading reporting: selectively and strategically reporting outcomes in various places in the article to present study results as being more favorable than the data warrants (i.e. discussing only significant results to distract the reader non-significant ones; no consideration of method limitations; etc.)

2.2. Study selection and data extraction

We performed a systematic search of Medline using PubMed to identify all pharmacovigilance disproportionality analyses using databases of spontaneous reports by healthcare professionals or patients. The search terms were “case-non case”, “case-no case” “disproportionality analysis”, “pharmacovigilance analysis” or “pharmacovigilance study”. Our search strategy enabled us to identify 435 articles, indexed in Medline between its inception and 1st January 2020. After screening titles and abstracts, 230 citations were considered eligible for inclusion. We mainly excluded articles because they were methodological studies (n=77), were not based on a pharmacovigilance database (n=50) or did not performed a disproportionality analysis (n=43). (Figure S1) Then we randomly selected 100 studies (listed in the supplementary material).

For each selected article, the presence of spin was independently assessed by 2 reviewers (AM, ML, BR, CK) and any disagreements were resolved by consensus. Suspected spin in each section of the article was classified according to the categories of spin described above. We also estimated the overall level of spin in each article: a high level of spin was defined as

an abstract or conclusion containing an inappropriate interpretation of the results (i.e. using causal language) and otherwise the articles was considered to have a low level of spin.

We also collected data on various covariables such as declared financial conflict of interest, year of publication, journal category, author characteristics and citation count.

2.3. Statistical analysis

Categorical data are expressed as frequencies and continuous data are presented using medians with interquartile ranges (IQR). Agreement between reviewers were assessed by Cohen's Kappa. Association between spin and each above-mentioned covariate were explored through logistic regression models, odds ratio (OR) with their 95% confidence intervals (95%CI) were estimated. A sensitivity analysis considering only articles with high levels of spin was conducted.

Given the exploratory nature of these analyses a p-value <0.05 was considered significant, without adjusting for the multiplicity of comparisons.

All analyses were performed using SAS[®] Studio, version 3.8 (SAS Institute Inc., Cary, NC, USA) and R (version 3.6.1).

3. RESULTS

3.1. Study characteristics

Among the 100 articles selected for inclusion, six did not have an abstract and seven did not have any identifiable conclusion section. The articles were published between 1997 and 2019, but 70% were published since January 2015. Sixty percent of the studies were published in pharmacology journals, and 40% in specialized medical journals. The median journal impact factor was 2.9 (2.2-3.7), and the median number of citations per article per year was 1.58 (0.7-3.1). In 24 studies, the authors reported a financial conflict of interest; the gender of the first and last authors were male, female and mixed for 47, 10 and 43 articles respectively.

3.2. Classification of spin

Among the 100 studies, 63 (67%), 56 (56%) and 51 (55%) had at least one type of spin in their abstract, in their main text or in their conclusion, respectively (Figure 1 and Table S1). The agreement between reviewers was moderate, with a Cohen's Kappa of 0.45 (95% CI, 0.29-0.62) for presence of spin in the results and of 0.73 (95% CI, 0.57-0.87) for spin in the

abstract. Forty articles were classified as containing a high level of spin (i.e. abstract and/or conclusion containing inappropriate interpretation of findings), and 41 containing a low level of spin. Overall, only 19 articles did not show any type of spin.

Each of the 3 categories of spin (inappropriate interpretation, inappropriate extrapolations and misleading reporting) included several spin strategies which are detailed in Table 1 with some illustrative examples extracted from the selected studies.

Inappropriate interpretation, inappropriate extrapolations and selective reporting were identified in the main text of 39, 27 and 40 articles respectively. Spin in titles and in results sections were exclusively inappropriate interpretation of findings (12% and 21% respectively), with terms such as “risk of” or “risks associated with” or results presented as ORs. Discussion sections mostly contained inappropriate interpretations (38%), and to a lesser extent inappropriate extrapolations (10%) and misleading reporting (12%). Misleading reporting, notably failing to acknowledge the limitations of disproportionality analyses, was the most frequent type of spin in abstracts (55%) and conclusions (37%). We also found inappropriate interpretations in 34% and 28% of the abstract and conclusions respectively, and inappropriate extrapolations, such as recommendations for clinical practice or comparisons of drug safety profiles in more than a quarter of the conclusions, and 16% of abstracts (Figure 2).

3.3.Factors associated with spin

As shown in Table 2, no association was found between the presence of spin and journal category (clinical vs pharmacology) (OR=1.18 (95% CI 0.42-3.31)), year of publication (OR=1.00 (95% CI 0.90-1.10)) , author gender (OR=0.26 (95% CI 0.03-2.27)), authors’ financials conflict of interests (OR=0.86 (95% CI 0.27-2.69)), journal impact factor (OR=0.90 (95% CI 0.79-1.02)) or article citation per year (OR= 0.96 (95% CI 0.83-1.11) The results were consistent when considering only articles with high level of spin.

4. DISCUSSION

To our knowledge, this is the first study to evaluate spin in published pharmacovigilance disproportionality analyses. Of the 100 studies evaluated, 63, 56 and 51 had at least one type of spin in their abstract, main text or conclusion respectively, and 40% used causal language to interpret their results in the abstract or conclusion section. Using causal claims to interpret findings is the most common type of spin in observational studies and is cornerstone of

interpretation of the results of pharmacoepidemiology and pharmacovigilance [14,15]. In assessing causal inference in randomized and non-randomized clinical trials, Li and colleagues found an overestimation of the strength of causal inference in the abstracts of non-randomized clinical trials.[16] Lazarus and colleagues, quantified spin in abstract of non-randomized studies and found that 53% of abstracts used causal language to describe their results. [12] Given the limitations inherent to spontaneous reporting databases (lack of exposure data, variable reporting of ADRs) and inherent to disproportionality analyses (inability to control for confounding, competition between drugs and events) drug-related risks cannot be quantified. Nevertheless, the concept of risk or suggesting a causal relationship, was present in the abstract or in the conclusion section of almost half of the 100 articles analyzed. The term ‘association’, was the most difficult to apprehend and generated many discussions among the team. Indeed, several authors used syntaxes such as “...was associated with an increase of reporting risk” or “we found an association between...”. While such interpretation of disproportionality results are not properly wrong, these formulations may evoke a causal association and could be replaced by less ambiguous terms such as “was associated with a signal of disproportionality” or “a signal of disproportionate reporting”. Furthermore, more than half of the abstracts failed to acknowledge any limitations of their findings. These findings are in agreement with previous reports of sub-optimal reporting of bias or confounding in observational studies of medical interventions. [17,18] This failure, in combination with an over-interpretation of results asserting a causal link, carries a significant risk of misleading readers.

Our findings are consistent with results of other studies, showing that spin is frequent in the entire medical literature [9,12]. A systematic review of 35 spin studies evaluated a median prevalence of spin of 67% (from 10% to 84%) in clinical trials, observational studies, diagnostic accuracy tests and systematic reviews [13]. It has been shown that the impact of spin in published articles is further enhanced by dissemination through press releases and news items [19,20] and leads to misinterpretation of the study findings by readers [21,22]. In pharmacovigilance studies, such practices may result in unjustified safety warnings that may affect physician or patients behaviours. [23] Spin in pharmacovigilance studies may arise from ignorance of the limitations of disproportionality analysis and spontaneous reporting system databases, imitation of previous practice, or willful intent to enhance sensationalism and newsworthiness of the results so as to be published in higher ranking journals. [8,24,25]

The actual impact of spin in pharmacovigilance studies on media release remains to be further explored and characterized.

We identified no association between spin and journal category (clinical vs pharmacology), year of publication, author gender, conflict of interest, journal impact factor or article citation per year in our study. While other studies found some sporadic associations, no factor is consistently and significantly associated with spin across studies. [13] Strikingly, the prevalence of spin has remained stable over the years despite a worldwide effort to limit misinterpretation or over interpretation of study results by authors appraising the evidence behind the results in published biomedical research [9]. Importantly, spin was not associated with higher citations per year or journal impact factor, which is reassuring with regards to the motives driving the publication and citation of pharmacovigilance studies.

The development of reporting recommendations, endorsed by journal editors, may help to reduce the level of spin in published pharmacovigilance disproportionality studies. We also encourage peer reviewers and journal editors to check for inappropriate use of causal language, especially in the abstract and manuscript conclusions. Although, to date, the only RCT aiming to reduce the prevalence of spin in biomedical literature by sending instructions to the authors during the submission process failed to demonstrate a significant impact. The education of authors and peer reviewers on the limits of disproportionality analyses may also be one of the key avenues for improvement [26].

Our study has several strengths and limitations. Since we conducted our study using a randomized sample of studies indexed in PubMed, our results should only be representative of disproportionality analyses published in journals indexed on this database. The assessment of spin is a subjective task, involve interpretation and multiple judgements of authors inevitably influenced by personal belief and context. To deal with this issue, two reviewers independently assessed each article according to a defined methodology and discrepancies were resolved by consensus. Our study did not determine whether spin strategies were intentionally used to give more credit to the results of the analyses of disproportionality or whether it reflects a poor grasp of disproportionality methods. Finally, the present study did not assess the impact of spin on the readers' interpretation of the results. Further studies should be conducted to answer this question.

5. CONCLUSION

We found that spin is frequent in publications of pharmacovigilance disproportionality analyses, notably in abstracts. Such studies are cornerstones for signal generation by researchers, stakeholders and agencies but do not allow risk quantification or causality assessment. The practice of spin in pharmacovigilance studies may therefore lead to readers' misinterpreting results and unjustified beliefs on the levels of evidence underlying links between drugs and adverse events.

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Charles Khouri: Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft, Writing - Review & Editing; **Marion Lepelley, Bruno Revol, Amelle Mouffak:** Investigation, Data Curation; **Matthieu Roustit, Jean-Luc Cracowski, Francesca Salvo, Antoine Pariente:** Writing - Review & Editing

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Table 1. Spin classification for disproportionality analyses assessing disproportionality signal in pharmacovigilance databases. Examples provided are from published abstract and full-texts from our sample.

Spin categories	Strategy used	Example
Inappropriate interpretation	Use of causal language	"This study shows a high risk of hepatic injuries with some selected [nonsteroidal anti-inflammatory drugs] NSAIDs." "our work shows that the oeso-gastro-duodenal risk is clearly higher than that previously suggested by the sole clinical trials"
	Tone inferring a strong result	"The results show significant incidence of [supraventricular arrhythmias] SVA, [ventricular arrhythmias] VA, [conduction disorders] CD, [heart failure] HF, hypertension, [central nervous system] CNS ischemic, and hemorrhagic events with ibrutinib, with numbers high enough to suggest that some of these [cardiovascular adverse drug reactions] CV-ADR may be under-represented in the published data. "
	Talk about odds ratio (OR) instead of reporting odds ratio (ROR)	"In comparison with other drugs in the database, liver injuries were inversely associated with exposure to [nonsteroidal anti-inflammatory drugs] NSAIDs, whatever the class of the drugs (OR 0.3 [0.3-0.4])."
Inappropriate extrapolations	Claiming the treatment is safe	"To the best of our knowledge, the present survey is the first to demonstrate the safety of MMF[mycophenolate mofetil], especially in pediatric renal transplant patients."
	Comparison of drug safety profiles	"The risk of dependence was similar for triptans and ergot derivatives and did not differ from that of benzodiazepines." "The risk of withdrawal syndrome appears to be greater with short half-life drugs such as paroxetine and venlafaxine."

"The safety profile of sclerosing agents significantly differs and should guide benefit-risk ratio assessment of such agents."

Provide recommendations for clinical practice "These findings can be used to update information used for prescriptions for pediatric patients."

"Accordingly, a cautious evaluation of [tumor lysis syndrome] TLS in clinical practice is recommended for patients receiving bortezomib-containing therapy."

"From a practical point of view, it underlines the importance to prescribe as DA [dopamine agonists] in Parkinsonian patients only non-ergot DA agonists, excluding ergot derivatives."

Misleading reporting Important limitations are not taken into account in the interpretation of the results.
Discussing only significant results to distract the reader from unfavorable ones

Table 2. Association between spin and author, article and journal characteristics. Results are presented as odds ratio (OR) and 95% confidence intervals (95% CI).

Characteristics	All level of Spin			High level of spin		
	OR	95% CI	p-value	OR	95% CI	p-value
Journal category						
Clinical vs. pharmacological	1.18	(0.42-3.31)	0.76	0.84	(0.37-1.91)	0.68
First and last authors' gender						
Male vs. Female	0.26	(0.03-2.27)	0.22	0.47	(0.12-1.87)	0.28
Author financial conflict of interest						
Yes vs. no	0.86	(0.27-2.69)	0.79	1.37	(0.54-3.47)	0.50
Journal impact factor	0.90	(0.79-1.02)	0.09	0.88	(0.73-1.06)	0.17
Article citation per year	0.96	(0.83-1.11)	0.54	0.97	(0.85-1.11)	0.65
Year of publication	1.00	(0.90-1.10)	0.93	0.95	(0.88-1.03)	0.24

Figure legend

Figure 1. Upset plot of the distribution of each spin category according to the article section

Figure 2- Prevalence of each spin category according to the article section

