PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Differences in Reporting Serious Adverse Events in Industry Sponsored Clinical Trial Registries and Journal Articles on Antidepressant and Antipsychotic Drugs – A Cross-sectional Study
AUTHORS	Hughes, Shannon; Cohen, David; Jaggi, Rachel

VERSION 1 - REVIEW

REVIEWER	Beate Wieseler Institute for Quality and Efficiency in Health Care, Im Mediapark 8, 50670 Cologne, Germany
REVIEW RETURNED	24-May-2014

GENERAL COMMENTS	General comment: Thank you for the consideration of my comments on an earlier version of the manuscript. I only have a few further comments. Introduction, page 5, lines 21-29 Your description of the format of clinical trials summaries posted on trial registries suggests that there is a clear standard for this type of document. From my point of view this is not the case, especially not for the registry you have investigated (clinicalstudyresults.org). For example, the registry report you are presenting as a supplement to your paper by far exceeds the ICH E3 guideline on the study synopsis (that is the section of ICH E3 the PhRMA document recommends for registry reports) by adding detailed data tables. I would recommend a more cautious statement on the format of trial summaries in registries. Methods section Page 7, lines 10-15: Journal articles The statement that there was an average of two publications per trial might be misunderstood as suggesting that all trials had journal publications. According to your data this is not the case. Page 9, lines 15-17 Please include a description of the categories of discrepant reporting used in your study. Did you only use the 3 categories presented in Table 5 or were there additional categories. What were the criteria for categorizing a discrepancy into a specific category (e.g. is seems to be difficult to distinguish between "differences in SAE reporting criteria used" and "apparent selective reporting of data")?

	Results section Page 9: Sample description Please include the percentage of trials in your sample for which a journal publication was available (overall and per drug). Page 12: Explanations for discrepant reporting What is the basis for the percentages used in this paragraph (e.g. there are 25% in which different study length was reported, is this percentage relating to 70 discrepant pairs?)? Please clarify. Please consider adding absolute numbers. Overall, the percentages do not seem to add up to 100%. Please include a statement on the missing discrepant pairs. Page 13, line 22 Please consider adding a new heading for the sections on removal of clinicalstudyresults.org Figure 1 Trial summaries excluded with reasons box: the reason “no or few trial summaries were posted” is difficult to understand; please re-consider (e.g. reports for drugs with no or few trials summaries posted)

REVIEWER	Norio Watanabe National Center of Neurology and Psychiatry, Japan
REVIEW RETURNED	31-May-2014

GENERAL COMMENTS	The study examined the degree of concordance in reporting serious adverse events (SAEs) from trials of antipsychotics and antidepressants among journal articles and online clinical trials summaries, and concluded that substantial discrepancies exist in SAE data between two sources. The study appears to be intriguing for clinicians and researchers attempting to obtain accurate knowledge of psychotropic pharmacotherapy. However, some points should be re-considered before publication. Abstract In the Objective subsection, the authors described the objective of the study as examining the degree of concordance in reporting adverse events from psychotropic drug trials. However, only antidepressant and antipsychotic trials were included. I personally recommend changing the objective to be narrower. I am curious about differences in reporting SAEs between antidepressants and antipsychotics. If word limit allows, it is better informative when the authors incorporate these into the Abstract. Introduction The authors mentioned that journal publications and clinical trial summaries posted on trial registries currently represent the primary information sources for clinicians and decision-makers regarding the safety and effectiveness of drug treatments. However, decision-makers can take advantage of data in regulatory agencies such as FDA. I do not think this sentence is precisely correct. In the introduction section, previous lliteratures on the same topic of the study should be reviewed and their limitations should be mentioned to clarify the rationale of the study.

	Methods The search results and the numbers of pairs included in the study should be stated in the Results section, not in the Methods. Results The link the authors provided for trial summaries (www.rxarchives.com) does not seem to exist.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Beate Wieseler

General comment: Thank you for the consideration of my comments on an earlier version of the manuscript. I only have a few further comments.

Introduction, page 5, lines 21-29
Your description of the format of clinical trials summaries posted on trial registries suggests that there is a clear standard for this type of document. From my point of view this is not the case, especially not for the registry you have investigated (clinicalstudyresults.org). For example, the registry report you are presenting as a supplement to your paper by far exceeds the ICH E3 guideline on the study synopsis (that is the section of ICH E3 the PhRMA document recommends for registry reports) by adding detailed data tables. I would recommend a more cautious statement on the format of trial summaries in registries.

AUTHORS' RESPONSE: The reviewer has rightly noted that some of the trial summaries provide substantially greater detail than others, exceeding ICH E3 guidelines. We revised the statement on page 5 in the Introduction, adding that the summaries are structured according to ICH E3 guidelines and that their "level of detail can vary substantially."

Methods section
Page 7, lines 10-15: Journal articles
The statement that there was an average of two publications per trial might be misunderstood as suggesting that all trials had journal publications. According to your data this is not the case.

AUTHORS' RESPONSE: We thank the reviewer for pointing out this potential cause of confusion. The 496 listed publications were counted across 172 of the 244 trials --- 72 trials thus had no publication of any kind listed. We hope we have clarified this in the Methods section by adding: "Of the 244 trial summaries, 72 (29.5%) listed no publication of any kind, 30 (12.3%) listed only one or more of the excluded publication types, and 142 (58.2%) listed at least one associated stand-alone journal article."

Page 9, lines 15-17
Please include a description of the categories of discrepant reporting used in your study. Did you only use the 3 categories presented in Table 5 or were there additional categories. What were the criteria for categorizing a discrepancy into a specific category (e.g. is seems to be difficult to distinguish between "differences in SAE reporting criteria used" and "apparent selective reporting of data")?

AUTHORS' RESPONSE: Our analysis of discrepant reporting was inductive in nature, so that the 3 categories we report emerged from the data. There were no additional categories that emerged from

this analysis. The last category, apparent selective reporting of data, was only assigned if the other two possible explanations were clearly not applicable. We have revised this explanation in the manuscript to read: “In each instance of discrepant reporting, we performed an in-depth inductive analysis involving a careful review of the trial summary and journal article to identify a possible explanation for the inconsistency. We then grouped the emerging patterns, which resulted in three categories (described in the results section): differences in study length or phase reported, differences in reporting criteria used, and apparent selective reporting of SAE data. Discrepancies were only assigned to the latter category after ruling out the other two explanations. No additional categories to explain discrepant reporting emerged from the analysis.”

Results section
Page 9: Sample description
Please include the percentage of trials in your sample for which a journal publication was available (overall and per drug).

AUTHORS’ RESPONSE: We added this information to the sample description by summarizing: “Overall, a stand-alone journal article was available for 58.2% of trials in this sample, though this varied by drug from a low of 27.6% for trials of ziprasidone to 72.9% for trials of duloxetine.” The number of trials per drug for which a journal publication was available is provided in Table 1, although we were unable to also include the percentage in this Table due to space constraints.

Page 12: Explanations for discrepant reporting
What is the basis for the percentages used in this paragraph (e.g. there are 25% in which different study length was reported, is this percentage relating to 70 discrepant pairs?)? Please clarify. Please consider adding absolute numbers. Overall, the percentages do not seem to add up to 100%. Please include a statement on the missing discrepant pairs.

AUTHORS’ RESPONSE: In line with the reviewer’s suggestion, we added absolute numbers to our percentages in this section. After re-calculating, we found that the numbers had not been adding up to 100% because 3 cases of discrepant reporting had been assigned to a “miscellaneous” category. We reviewed these 3 cases and were able to assign them to an appropriate category. One was added to differences in reporting criteria, one to omission of SAE data, and one to the minority of cases where the journal article reports a higher number than the trial summary. The numbers now add up to 100%.

Page 13, line 22
Please consider adding a new heading for the sections on removal of clinicalstudyresults.org

AUTHORS’ RESPONSE: We added the following heading to this section: Post Hoc Analysis of Clinical Trial Summaries on Clinicaltrials.gov

Figure 1
Trial summaries excluded with reasons box: the reason “no or few trial summaries were posted” is difficult to understand; please re-consider (e.g. reports for drugs with no or few trials summaries posted)

AUTHORS’ RESPONSE: We made the relevant change in language on Figure 1. We further revised Figure 1 to bring additional clarification regarding some of the reviewer’s previous comments. Specifically, we added a search results box to this Figure that details how many trial summaries had no publications, had only excluded publications, and had at least one stand-alone journal article.

Reviewer Name: Norio Watanabe

The study examined the degree of concordance in reporting serious adverse events (SAEs) from trials of antipsychotics and antidepressants among journal articles and online clinical trials summaries, and concluded that substantial discrepancies exist in SAE data between two sources. The study appears to be intriguing for clinicians and researchers attempting to obtain accurate knowledge of psychotropic pharmacotherapy. However, some points should be re-considered before publication.

Abstract

In the Objective subsection, the authors described the objective of the study as examining the degree of concordance in reporting adverse events from psychotropic drug trials. However, only antidepressant and antipsychotic trials were included. I personally recommend changing the objective to be narrower.

I am curious about differences in reporting SAEs between antidepressants and antipsychotics. If word limit allows, it is better informative when the authors incorporate these into the Abstract.

AUTHORS' RESPONSE: We agree with the reviewer and made the relevant change in the Abstract Objective.

Introduction

The authors mentioned that journal publications and clinical trial summaries posted on trial registries currently represent the primary information sources for clinicians and decision-makers regarding the safety and effectiveness of drug treatments. However, decision-makers can take advantage of data in regulatory agencies such as FDA. I do not think this sentence is precisely correct.

AUTHORS' RESPONSE: We again agree with the reviewer on this point and have added to this sentence in the Introduction "…and data from regulatory agencies such as the U.S. Food and Drug Administration (FDA)…"

In the introduction section, previous literatures on the same topic of the study should be reviewed and their limitations should be mentioned to clarify the rationale of the study.

AUTHORS' RESPONSE: In response to the reviewer's suggestion here, we have added a couple sentences to the Introduction to summarize the rationale of the study based on the previous literature. Since we detail this literature as it relates to our study's findings in the Discussion, we have not added this information to the Introduction. We believe, however, that the sentences we did add to the Introduction address the reviewer's primary suggestion about clarifying the rationale of the study. The added sentences read: "While previous research has demonstrated that harms data are less completely reported in journal articles than clinical trial summaries, these studies provide primarily quantitative counts of reporting practices. The present analysis seeks to elaborate the nature of quantitative and qualitative differences in SAE reporting, and possible explanations for reporting discrepancies."

Methods

The search results and the numbers of pairs included in the study should be stated in the Results section, not in the Methods.

AUTHORS' RESPONSE: We revised the manuscript accordingly by moving the description of search results to the first section of the Results (titled: "Search Results and Sample Selection").

Results
The link the authors provided for trial summaries (www.rxarchives.com) does not seem to exist.

AUTHORS' RESPONSE: The link to the website is now functioning and the appropriate hyperlink has been added to the manuscript.