PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Characteristics of Pharmacist's interventions triggered by prescribing errors related to computerized physician order entry in French hospitals: a cross-sectional observational study
AUTHORS	Videau, Manon; Charpiat, Bruno; Vermorel, Céline; Bosson, J.L; Conort, Ornella; Bedouch, Pierrick

VERSION 1 – REVIEW

REVIEWER	Dabaghzadeh, Fatemeh Kerman University of Medical Sciences
REVIEW RETURNED	01-Dec-2020

GENERAL COMMENTS	This study is about characterizing pharmacist interventions triggered by prescribing errors identified as system-related errors in French hospitals. The manuscript is well-written.The subject of study is not new. The major problem regarding this manuscript is system-related errors. It is necessary to explain it better with more examples. I cannot understand the difference between system-related errors and other errors in this study. Please explain these errors in details.

REVIEWER	Abdel-Qader, Derar H. University of Petra
REVIEW RETURNED	13-Dec-2020

GENERAL COMMENTS	Thanks for your efforts. The paper lacks novelty and coherency. Further, what about the validation of the data collection?!

REVIEWER	Turner, Emily NHS Leeds Clinical Commissioning Group
REVIEW RETURNED	15-Dec-2020

GENERAL COMMENTS	Interesting question well addressed with big data. I think it important to make it clear to the reader how common reporting via Act-IP is. Is this done by all hospital pharmacists for every intervention they make or just by some or for interventions they select for recording? It was not clear to me as a non-French pharmacist. This would address the limitations of the data set better and describe any potential reporting bias that may impact on results.

REVIEWER	PAGES, Arnaud CHU Toulouse, Pharmacy
REVIEW RETURNED	30-Mar-2021

GENERAL COMMENTS	Thank you for the opportunity to review this study on the characteristics of Pharmacist's interventions triggered by prescribing errors related to CPOE. This research identifies some interesting facts about pharmacist interventions related to system-related errors and presents some considerations to those findings. Abstract: 1. Could you rephrase the sentence in the participants section to improve its understanding? 2. Could you define the method of calculation of the PISRE ratio? If the PISRE ratio is the ratio of PISREs to PIs unrelated to SREs, it should not be expressed as a percentage. 3. Could you add the main p-values in the results section? Strengths and limitations of this study: 1. Could you specify if the sample used in your study is representative of French hospitals? Introduction: 1. Page 5, line 15: Could you clarify if the numbers in the brackets are the 95% confidence interval? 2. Page 6, lines 21-25: I think it would have been more interesting to take as primary objective the analysis of factors associated with PISREs (versus PIs unrelated to SREs) and as secondary objective, the analysis of factors associated with PI acceptance for the subgroup of PISREs. Methods: 1. Could you verify that your study follows the STROBE guidelines and mention it in the method section? 2. Page 6, lines 38-41: Did the pharmacists give their consent to use their declarative data? If it was the case, please add this information in the article. 3. Page 7, lines 32-41: You have performed a bivariate analysis to compare PISREs with some patient and prescription characteristics (chi2 tests). This analysis alone seems difficult to interpret because it was not controlled for potential confounders. I think that it would be interesting to also perform a multivariate analysis (response variable: PISREs (versus PIs unrelated to SREs)). You could use a mixed model to deal with the hierarchical structure of the data (hospital/pharmacist/PIs). 4. Page 7, lines 32-41: The same type of statistical analysis could be used for the acceptance of PISREs. 5. Page 7, lines 32-41: You mentioned that the data was declarative so missing data were expected. How do you deal with this issue? Results:

	1. Could you provide more information on the hospitals involved (public/private, number of beds, secondary care/tertiary care, types of medical activities (rehabilitation care, surgery, geriatrics, emergency care, intensive care,...), number of clinical pharmacists per bed, time since implementation of CPOE,...)? It would be interesting to compare the hospitals characteristics in your sample with the hospitals characteristics in France to know if your sample was representative and if your results were generalizable. 2. Could you provide more information on the patients (age, gender, number of drugs,…)? Tables: 1. Table 1: The p-value for “drug related problem” and “type of intervention” rows are missing. Could you add it? 2. Table 1: Could you provide the percentages for each categories? 3. Table 1: Could you add an additional column with the numbers and percentages for “PIs unrelated to SREs”? 4. Table 1: Could you define the method of calculation of the PISRE ratio in the legend? 5. Table 2: Could you put table 2 in the appendix instead? 6. Table 2: Could you change the term “generic name” by “international nonproprietary names”? Figures: 1. Figure 1, You should use another acronym than PIs to name the PIs unrelated to SREs.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Fatemeh Dabaghzadeh, Kerman University of Medical Sciences Comments to the Author:
This study is about characterizing pharmacist interventions triggered by prescribing errors identified as system-related errors in French hospitals. The manuscript is well-written.The subject of study is not new.

The major problem regarding this manuscript is system-related errors. It is necessary to explain it better with more examples. I cannot understand the difference between system-related errors and other errors in this study. Please explain these errors in details.

Authors: The list of this type of errors is endless. This is illustrated in the report entitled “Computerized Prescriber Order Entry Medication Safety (CPOEMS): Uncovering and Learning From Issues and

Errors. US Food and Drug Administration; FDA; Brigham and Women's Hospital; Harvard Medical School; Partners HealthCare January 13, 2016." Especially Appendix

C: Revised MedMarx Taxonomy p.12 and Appendix D: BWH MedMarx Coding Guide p.18. available at https://psnet.ahrq.gov/issue/computerized-prescriber-order-entry-medication-safety-cpoems-uncovering-and-learning-issues and https://www.fda.gov/media/95234/download.

In the revised version among examples of PISRE and drug by drug-related problems given Table 2 (Appendix 2 in the revised version), we explained two of them in details in the revised manuscript.

Prescription errors can be the same whether they are handwritten prescriptions or computer-assisted prescriptions. Indeed, the combination of amiodarone and escitalopram can appear on handwritten prescription because of prescriber's lack of knowledge. With CPOE, Clinical

Decision Support System (CDSS) tool can alert on drug-drug interaction. However, high

frequency of alerts and dozens of daily interruptions for clinicians are responsible of "alert fatigue" and practitioners override alerts [1].

We can also find duplicate orders, meaning the same drug is prescribed twice. With predefined order set, it is common to have 8 grams of paracetamol per day prescribed. Duplication errors are partially explained by the fact that many screens are required to view patient medications, making intrinsically difficult to spot duplicates [2].

[1] van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc. 2006 Mar-Apr;13(2):138-47.
"amiodarone and escitalopram combination contra-indicated: risk of "torsade de pointes" not modified during drug interaction alert with Clinical Decision Support System (CDSS)". Low specificity (inability to prevent irrelevant alerts) may result in a deluge of alerts and subsequently 'alert fatigue' (important alerts being ignored along with clinically unimportant ones).

[2] Wetterneck TB, Walker JM, Blosky MA, Cartmill RS, Hoonakker P, Johnson MA, Norfolk E, Carayon P. Factors contributing to an increase in duplicate medication order errors after CPOE implementation. J Am Med Inform Assoc. 2011 Nov-Dec;18(6):774-82.

Wetterneck highlighted that in one US hospital, duplicate medication ordering errors increased after CPOE implementation (pre: 48 errors, 2.6% total; post: 167 errors, 8.1% total; $p<0.0001$). Most post-implementation duplicate orders were either for the identical order or the same medication [2].

Reviewer: 2

Dr. Derar H. Abdel-Qader, University of Petra

Comments to the Author:

Thanks for your efforts. The paper lacks novelty and coherency. Further, what about the validation of the data collection?!

Authors: in 2006, three of the authors of the manuscript (BC, OC, PB) published a coding system for pharmacist's interventions [reference 20 in the manuscript]. The validation process was based on Kappa coefficient of concordance to assess the level of agreement between experts for codification of drug related problems (DRPs) and interventions. The level of concordance observed in the validation was 0.76 for DRPs and 0.89 for the type of intervention. The level of concordance between users was considered as satisfactory, allowing the use of the tool in daily clinical pharmacy practice. Readers can therefore refer to citation 20.

Reviewer: 3

Dr. Emily Turner, NHS Leeds Clinical Commissioning Group Comments to the Author:

Interesting question well addressed with big data.

I think it important to make it clear to the reader how common reporting via Act-IP is. Is this done by all hospital pharmacists for every intervention they make or just by some or for interventions they select for recording? It was not clear to me as a non-French pharmacist. This would address the limitations of the data set better and describe any potential reporting bias that may impact on results.

Authors: Annually, our team analyzes the quantitative and qualitative evolution of the data recorded on the Act-IP © website (unpublished data). These analyzes show in particular that data entry can be total for a given pharmacist over a given period. It can also stop during a change of assignment. Some with whom we spoke point out that the regularity of data entry is conditioned by their workload. Many pharmacists record prospectively their data on paper on a daily basis and thereafter register them by series on Act-IP © website. Also for some of them, the data entry is irregular or is performed with a certain delay. We consider that these elements have consequences on the quantity of recorded data but not on their quality. We have specified this in the paragraph “5.7. Limits”.

Our team [references available at
https://pubmed.ncbi.nlm.nih.gov/?term=charpiat+b+bedouch+p+allenet+b+conort+o&sort=dat

e&size=200 and others [https://pubmed.ncbi.nlm.nih.gov/?term=act-ip&sort=date&size=200] have published several analyzes of the content of the Act-IP© website. These have shown that all types of drug related problems and interventions are collected and recorded.

From a general point of view, the major determinant of a PI is the knowledge of the pharmacist who analyzes the prescription. It is this knowledge that enables him to detect a problem. Thus, a PI that is considered as necessary and is not performed means that it is not recorded and will be absent from the database. This happens when a doctor routinely makes a certain type of prescribing error and the pharmacist fails to detect it due to knowledge deficit. It has been shown that, if several pharmacists analyze the same drug prescriptions, they don't all track down the same problems. One paper highlighted that the frequency of intervention could vary by a factor of one to ten from one pharmacist to another. In another study involving 57 hospital pharmacies, the mean percentage of detected prescribing errors was 59%, with a broad range of 7–88% between pharmacies [Find details in references 1]. This point was already covered in the discussion.

Some might argue the fact that data are recorded on a voluntary basis can be a source of bias. However, as illustrated by other publications, studies based on data recorded on a voluntary basis remain relevant to examine the nature of safety problems involving a broad range of systems and brands across diverse implementation contexts [2,3].

[1] Charpiat B, Bedouch P, Tod M, Allenet B. Classifying pharmacists' interventions recorded in observational databases: Are they all necessary and appropriate? Res Social Adm Pharm. 2017 Nov;13(6):1184-1185.

[2] Magrabi F, Ong MS, Runciman W, Coiera E. Patient safety problems associated with heathcare information technology: an analysis of adverse events reported to the US Food and Drug Administration. AMIA Annu Symp Proc. 2011;2011:853-7.

[3] Magrabi F, Ong MS, Runciman W, Coiera E. Using FDA reports to inform a classification for health information technology safety problems. J Am Med Inform Assoc. 2012 Jan-Feb;19(1):45-53.

Reviewer: 4

Dr. Arnaud PAGES, CHU Toulouse

Comments to the Author:

Thank you for the opportunity to review this study on the characteristics of Pharmacist's interventions triggered by prescribing errors related to CPOE. This research identifies some interesting facts about pharmacist interventions related to system-related errors and presents some considerations to those findings.

Abstract:

1. Could you rephrase the sentence in the participants section to improve its understanding?

Authors: we modified according to reviewer's suggestion

2. Could you define the method of calculation of the PISRE ratio? If the PISRE ratio is the ratio

of PISREs to PIs unrelated to SREs, it should not be expressed as a percentage.

Authors: The PISRE ratio was estimated relative to the total number of PIs.

3. Could you add the main p-values in the results section?

Authors: We added the main p-values

Strengths and limitations of this study:

1. Could you specify if the sample used in your study is representative of French hospitals?

Authors: We cannot because French data regarding hospitals and pharmacy activities and staffing at a national level are lacking. At our knowledge, studies similar to references [1-3] remain to be performed in our country.

[1] Bond CA, Raehl CL, Franke T. Clinical pharmacist staffing in United States hospitals. Pharmacotherapy. 2002 Nov;22(11):1489-99.
[2] Canadian Society of Hospital Pharmacy. Hospital Pharmacy in Canada Report 2016/17 84 pages http://www.hospitalpharmacysurvey.ca/
[3] Schneider PJ, Pedersen CA, Ganio MC, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: Workforce-2018. Am J Health Syst Pharm. 2019 Jul 18;76(15):1127-1141.

Introduction:

1. Page 5, line 15: Could you clarify if the numbers in the brackets are the 95% confidence interval?

Authors: we clarified

2. Page 6, lines 21-25: I think it would have been more interesting to take as primary objective the analysis of factors associated with PISREs (versus PIs unrelated to SREs) and as secondary objective, the analysis of factors associated with PI acceptance for the subgroup of PISREs.

Authors: We consider this point to be minor because it is not likely to fundamentally change the

whole article.

Methods:

1. Could you verify that your study follows the STROBE guidelines and mention it in the method section?

Authors: The STROBE checklist is added with the revised manuscript.

2. Page 6, lines 38-41: Did the pharmacists give their consent to use their declarative data? If it was the case, please add this information in the article.

Authors: we clarified. To be registered onto the Act-IP© website, pharmacists had prior to accept terms and conditions and allowed the use of their data for analysis.
2. Page 7, lines 32-41: You have performed a bivariate analysis to compare PISREs with some patient and prescription characteristics (chi2 tests). This analysis alone seems difficult to interpret because it was not controlled for potential confounders. I think that it would be

interesting to also perform a multivariate analysis (response variable: PISREs (versus PIs unrelated to SREs)). You could use a mixed model to deal with the hierarchical structure of the data (hospital/pharmacist/PIs).

Authors:

This is indeed one of the limitations of this study. When analyzing the data, we attempted to perform a multivariate analysis using an exploratory approach to identifying risk factors (stepwise backward elimination). However, goodness of fit of the model was unsatisfactory. We hypothesized that the variables used to build the model were not sufficient and that it was probable that other variables (not available from Act-IP) could play a role in the occurrence of PISREs.

3. Page 7, lines 32-41: The same type of statistical analysis could be used for the acceptance of

PISREs.

Authors: We cannot for the same reasons as those explained above.

4. Page 7, lines 32-41: You mentioned that the data was declarative so missing data were expected. How do you deal with this issue?

Authors: We decided to exclude of the analysis pharmacist's interventions with missing data. Therefore pharmacist's interventions without drug involved were excluded from preliminary sample.

Results:

1. Could you provide more information on the hospitals involved (public/private, number of beds, secondary care/tertiary care, types of medical activities (rehabilitation care, surgery, geriatrics, emergency care, intensive care,...), number of clinical pharmacists per bed, time since implementation of CPOE,...)?

Authors: As these information are partially available in Act-IP over the period of analysis, it was

not relevant to present it in the manuscript.

It would be interesting to compare the hospitals characteristics in your sample with the hospitals characteristics in France to know if your sample was representative and if your results were generalizable.

Authors: We cannot for the same reasons as those explained above.

2. Could you provide more information on the patients (age, gender, number of drugs,…)?

Authors: During the design phase of this work, we considered that these data would not be relevant to achieve the objective we defined. These data were therefore excluded from the initial data set.
Tables:

1. Table 1: The p-value for "drug related problem" and "type of intervention" rows are missing. Could you add it?

Authors: we added.

2. Table 1: Could you provide the percentages for each categories?

Authors: The ratio corresponds to the percentage. For the sake of clarity, we have chosen not to overload the table.

3. Table 1: Could you add an additional column with the numbers and percentages for “PIs unrelated to SREs”?

Authors: For the sake of clarity, we have chosen not to overload the table. PIs unrelated to SREs can be found by simple calculation and are not the main focus of our study.

4. Table 1: Could you define the method of calculation of the PISRE ratio in the legend?

Authors: Done

5. Table 2: Could you put table 2 in the appendix instead?

Authors: Thank you for this suggestion. We put this table in the Appendix 2

6. Table 2: Could you change the term “generic name” by “international nonproprietary names”?

Authors: We modified as suggested.

Figures:

1. Figure 1, You should use another acronym than PIs to name the PIs unrelated to SREs.

Authors: Thank you for this suggestion. We modified the acronym.

VERSION 2 – REVIEW

REVIEWER	PAGES, Arnaud CHU Toulouse, Pharmacy
REVIEW RETURNED	27-Jul-2021

GENERAL COMMENTS	Thank you for the opportunity to review the modifications of the study on the characteristics of Pharmacist’s interventions triggered by prescribing errors related to CPOE. There would be just 2 small points to change: 1) There are two missing p-values in Table 1 (for "drug related problem" and "type of intervention"). Could you add them? 2) You wrote PIRSE instead of PISRE in the sentence "For our analysis, PIRSEs were classified according to the HAS status of the CPOE system (certified versus not certified)". Could you change the term?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

Dr. Arnaud PAGES, CHU Toulouse

Comments to the Author:

Thank you for the opportunity to review the modifications of the study on the characteristics of Pharmacist's interventions triggered by prescribing errors related to CPOE.

There would be just 2 small points to change:

1) There are two missing p-values in Table 1 (for "drug related problem" and "type of intervention"). Could you add them?

Authors: We modified as requested.

2) You wrote PIRSE instead of PISRE in the sentence "For our analysis, PIRSEs were classified according to the HAS status of the CPOE system (certified versus not certified)". Could you change the term?

Authors: Done

Reviewer: 4

Competing interests of Reviewer: No competing interests to report.