Author's response to reviews

Title: Evaluating Adverse Drug Event Reports in Administrative Data of Emergency Department Patients: A Validation Study

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Author's response to reviews: see over
Re: MS 1017563038830876 Evaluating Adverse Drug Event Reports in Administrative Data of Emergency Department Patients: A Validation Study

Dear Dr. Jones,

Thank you for the reviewers’ thoughtful comments on our paper. We have revised the manuscript according their comments, and respond to their concerns below. Below, we list the reviewer comments in the order of their appearance.

We have also corrected a coding error that we found when reviewing our SAS codes as a result of this review process. Therefore, you will find corrections in the results sections, none of which have significantly impacted our results.

We have attached an Excel spreadsheet to this communication. The spreadsheet contains the set of ICD-10 codes that we used to search the administrative data for adverse drug events with.

Thank you again on behalf of the investigative team, for providing us with an opportunity to revise and improve our manuscript.

We look forward to hearing from you again.

Sincerely,

Corinne Hohl
Referee 2:
1. A more meaningful discussion should be had in this paper (in the Discussion) regarding the essential and important role of the well-trained pharmacists used in this study. The reason there is a high and accurate rate of ADE in this study is due almost entirely by the fact that pharmacist was obtaining detailed history and providing an accurate assessment of medication-related relationship to the ED visit. This must be further described and highlighted in the study to not only explain the rate of ADE identified but also to promote the identification issue the authors correctly identify as important in the ED.

We have edited the manuscript to highlight the important contributions of the clinical pharmacists in this study (see page 15, 1st paragraph).

Referee 1:
1. First, the authors must re-phrase the title, abstract and text to indicate that they are attempting to identify “medication-related problems” (rather than adverse drug events) using ICD-10 administrative data. While there is some variation in definition of ADEs, the generally accepted definition is “an injury resulting from the use of a drug” which at minimum requires the presence of a drug (author’s ref 29-…). Four types of circumstances included by the authors (adverse drug reactions, drug interactions, drug use without indication, and high dose) are likely harms from use of the drug, and the authors should explicitly define each of these types of events. On the other hand, the other types of circumstances included by the authors -- low dose, need to add drug, noncompliance, and wrong drug -- may be related to low quality medical care but should not be considered “harm from use of a drug” (and if included also need explicit definition). If giving a “low dose” or needing to “add a drug” is considered an ADE, then every patient with hypertension who requires dose titration or addition of a second agent experiences multiple ADEs in the course of normal care. If “wrong drug” is an ADE, then every time empiric antibiotic therapy is changed based on culture and susceptibility results an ADE has occurred. The most obvious problematic circumstance identified by the authors and classified as an ADE is “noncompliance”. How can a drug which is not being taken by the patient be causing drug-induced patient harm? If the failure to take a drug is an ADE, then every asthma flare may be considered an ADE from inadequate treatment with anti-inflammatory medications. Indeed, in the authors’ previous work they highlight a case in which a 27 year-old was non-compliant with their steroid inhaler and had an asthma flare as an ADE (cited as reference 21, although it appears that the authors do not have the correct title of the article… In summary, while all of these circumstances may involve failure of “ideal” medication use, they are not ADEs as generally understood by clinicians, drug safety regulators, or most patient safety researchers. In fact, in a number of the author’s previous studies, the terminology “medication-related problems” (Ann Emerg Med. 2010;55(6):493-502) or “medication-related visits” (ref. 12) is used.

We thank reviewer 2 for highlighting the complexity and variation in the use of the terminology of adverse drug events, and have made edits to the manuscript to reflect this discussion.

Nebeker et al.1 (ref 29) present at least four definitions used for adverse drug events, including the definition preferred by reviewer 2, “harm caused by the use of a drug”, which Nebeker et al. explicitly qualify in their manuscript with its effective definition in practice: “harm caused by a drug or the inappropriate use of a drug”. We have edited our definition to clarify that we also included “inappropriate use” of a drug (see edited Definitions, page 8). Please note further that in Nebeker et al’s preferred definition of adverse drug events (on page 797 of his paper, and the
definition of the Institute of Medicine) adverse drug events are defined as “an injury resulting from medical intervention related to a drug”. Nebeker et al. specifically state that “the term adverse drug event includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy).” Thus, the term “use of” does not imply “exposure to”, but rather refers to the utilization of a drug in clinical practice. Inclusion of drug withdrawal is also consistent with Edwards et al.’s adverse drug reaction classification. 2 As a detailed discussion of adverse drug event terminology is beyond the scope of our manuscript, we have provided more detail about the definition we used (see Definitions, Pages 8 & 9), the pharmacists’ prospective classification of the etiology of the adverse drug events we studied (Appendix C), and the rationale for our choice of a broad definition (see Discussion, Page 17 & 18).

Clinicians practicing in emergency departments commonly see events due to untreated indication (e.g., lack of appropriate anticoagulation therapy in a patients with atrial fibrillation presenting with stroke), inappropriate dosing (e.g., reduction in a dose of furosemide leading to pulmonary edema requiring positive pressure ventilation), or noncompliance with medications (e.g., noncompliance with asthma medications leading to a flare, or noncompliance with insulin leading to diabetic ketoacidosis, etc.). While these events may not be of great interest from a pharmacovigilance and regulatory body perspective, for whom adverse drug reactions are most relevant, these events are relevant from the patient’s perspective (who suffers harm), from the emergency clinician’s perspective (who treats the event to minimize symptoms and prevent recurrence), and from the administrator’s, payer’s and health services/patient safety researcher’s perspective (as this causes health services utilization and increases cost, and some might be preventable). Therefore, we believe that understanding to what extent administrative data may be used identify and track these events is relevant. We have deliberately attempted to highlight our analysis of adverse drug reactions as we agree that adverse drug reactions may be of greater interest to the pharmacovigilance and/or drug regulatory bodies.

We believe that using the term medication/drug-related problem instead of adverse drug events would be misleading: While most adverse drug events are indeed preceded by a medication-related problem, 3 only few medication-related problems result in adverse drug events, and most remain only “potential adverse drug events”. In fact, medication-related problems are considered by some authors to be synonymous with the term potential adverse drug event. We explicitly stated in our definition of adverse drug events that only events presenting with symptoms, signs or abnormal laboratory values would be included in our definition. In addition, to safeguard against overcalling medication-related problems adverse drug events, both the pharmacist and treating emergency physician had to agree (after independent and blinded assessment) on the occurrence of an adverse drug event. In the case of any uncertainty or disagreement, an independent committee consisting of a medical toxicologist (a physicians) and pharmacist who were otherwise not involved in the study adjudicated the case using an explicit and pre-defined algorithm (Appendix A).

As all adverse drug reactions and adverse drug events are, by definition, medication or drug-related, we do not believe that our wording is inconsistent with our previous work.

Please note that have corrected the title of the reference. 4 Thank you for pointing out this error.

2. Second, a comparison of the data reported in this manuscript with data reported in a previously published article by the authors from what appears to be the same cohort of patients, from the
same hospitals, over the same time period (reference 21) is difficult to reconcile. A slight difference in the total study cohort (1571 vs. 1591) might be explained by slightly different inclusion dates,…

This is indeed the same cohort of patients. The difference in the number of included patients is 17 (1591 in the original study\(^4\) versus 1574 in the present study). We were unable to resolve the data linkage between the research and administrative dataset in 17 patients. This is explained in the Methods section (page 6, 1\(^{st}\) paragraph) and in the patient flow diagram (Figure 1).

… however, the published article (cited throughout the methods section) identified 131 outcomes/ADEs while the current manuscript identified 221 outcomes/ADEs. From the method section of the manuscript which heavily cites reference 21, it appears that both studies use the same “criterion standard”, but is this truly the case? In addition to discrepancy in the total numbers of ADEs, data reported on the relationship to chief complaint and classification of types of ADEs in the published article (Table 2) and this manuscript (Table 3) are hard to correlate as well. This substantial discrepancy in assessment of the primary outcome of ADEs must be addressed by the authors. Are the cohorts completely different? If so the authors must clarify in the methods section. Are there substantial differences in the assessment of outcomes/ADEs between the two papers? In other words, are certain types of ADEs (e.g., “wrong drug” or “need to add a drug”) included in the “criterion standard assessment” of this manuscript but not included in the “criterion standard” in the previously published article? If the “criterion standard” for ADE identification is flexible, how can it be used as the basis for assessing validity of ICD codes for identifying ADEs?

We would like to clarify how the present study relates to its parent study from which this cohort is derived:\(^4\) In our prior work, we defined adverse drug events as “untoward and unintended events arising from the use of prescription or over-the-counter medications”.\(^4\) In the present study, in an attempt to be more specific about the types of events we included, we specified the definition of “event” to include only “symptoms, signs or abnormal laboratory values” arising from the use of prescription or over-the-counter medications. While the data collection protocols of the parent study were explicit about this, we had not provided as specific a definition as possible in the manuscript of the parent study. We amended the definition for this present manuscript in order to be more explicit about the types of events included, and have also, in light of the concerns above, further clarified the definition to be explicit about the fact that the inappropriate use of medications was also included in our definition (in response to reviewer 2, comment 1). Thus although the wording of the definition is different in both manuscripts, these changes were only made to clarify and specify the definition further, but did not result in the inclusion of different patients. The outcome assessment protocol was the same for both studies and is detailed in a new Appendix A.

We asked pharmacists to classify all adverse drug events found using the taxonomy put forth by Hepler and Strand, as this taxonomy is commonly used in clinical pharmacy practice (Appendix C) and categorizes the events according to their etiology.\(^3\) The rationale for this categorization is that drug-related morbidity, including adverse drug events, are often preceded by a drug-related problem.\(^3\)

In the clinical decision rule derivation study, from which this cohort of patients is derived, we collected data on all the adverse drug events (and outcomes presented in the present study), and attempted to derive derived clinical decision rules for all adverse drug events (all categorizations
of the Hepler & Strand taxonomy), but this was not possible. We had stated a priori in our grant application that we would attempt to derive clinical decision rules for two narrower categorizations as well, one being moderate and severe adverse drug reactions, and the other encompassing moderate and severe adverse drug reactions or events due to noncompliance, a prescription error, drug withdrawal, or a drug interaction. Thus, the clinical decision rule derivation study represents a subset of the events analyzed in the present study. This is why the numbers of events listed is different.

We have acknowledged the limitation around the existing inconsistency of adverse drug event definitions as a limitation to our study (Discussion, Page 19, 1st paragraph).

3. Third, the authors say their objective is to determine the proportion of ADEs diagnosed at point-of-care that can be identified by ICD-10 coding. However, based on previous work by the authors, the treating clinician himself/herself did not recognize many instances to be ADEs, as defined by the authors, as such (Do emergency physicians attribute drug-related emergency department visits to medication-related problems? Ann Emerg Med. 2010 Jun;55(6):493-502). How could administrative coding be expected to identify a clinical condition that the treating clinician himself/herself does not identify and document as such? The authors should show an analysis of the physician-diagnosed ADEs that were also identified using ICD-10 codes and not only the analysis based on external “criterion standard” determination after review by another physician or pharmacist to determine ADEs.

As part of the study protocol (see new Appendix A), the pharmacists had to disclose all suspected adverse drug events that were not already documented in the chart to the treating emergency physician before the patient left the emergency department. This was required by our Ethics board in order to maximize patient safety. The adjudication committee did not identify any additional adverse drug events after the end of the patient’s visit, and was tasked only with reviewing those charts in which either the pharmacist or physician had already raised the possibility of an adverse drug event. The objective was to ensure, through adjudication by an independent committee, that events were not overcalled as adverse drug events. Thus, all identified and suspected events were disclosed to treating physicians before the charts were made available for coding. Therefore, lack of recognition of adverse drug events is unlikely to have contributed to our findings. We believe it is more likely that poor documentation contributed. We did not retain the physician’s diagnosis in our electronic database, as this was not the objective of the current study. We have edited the discussion section to reflect this (Discussion, page 15).

4. Fourth, code categories and C, D, E may be too insensitive to be useful. It is hard to determine, however, because the authors do not include a list of the ICD codes which they used. They do cite references which they state that they adapted; however, without a listing of the ICD codes used it is impossible to interpret analyses based on C, D, and E categories. Ideally the codes for categories A and B would be listed as well, but at least a reader could reproduce A and B categories from the description in the table, while it is impossible for the reader to guess how the authors might have chosen to select or adapt from references 26 and 27.

We have attached a spreadsheet with the code set we used, and encourage its publication as an appendix. Please see our edits to the Methods section (Page 7) highlighting some of the codes we used to pick up adverse drug events. We have provided more examples of the code categories in an edited Table 1.
5. Fifth, the authors might have neglected key ICD-10 codes for "Drugs, medicaments and biological substances causing adverse effects in therapeutic use" (Y40-Y59). The Y codes are not listed in manuscript table 1, and are probably the absolutely most critical codes for identifying ADEs. The authors should explicitly state that these codes are included. If they are not included this is a fundamental flaw in the analysis.

The Y40-59 external cause codes were included in our code set. We have edited the Methods to state this (Methods, Page 7, 1st paragraph), and to highlight some of the other codes we used.

6. Finally, without a specific ICD code for non-compliance, assessing validity of ICD coding for identifying such events is unreasonable. To this reviewer's knowledge, there is no ICD-10 code for non-compliance, but this should be stated by the authors in the manuscript. If there is a code for noncompliance, then the authors should explicitly identify it. Without a non-compliance code, it is virtually impossible for ICD codes to identify cases of non-compliance because the consequence of non-compliance is simply the progression of virtually any underlying disease condition (e.g., asthma, hypertension, skin infection, or even ACS if non-compliant with antiplatelet agent or cholesterol agent?).

The ICD-10 coded used to indicate noncompliance is Y66: Nonadministration of medical or surgical care. It is included in our code set (Methods, Page 7 and Table 1).
REFERENCES


