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
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Re: Authors’ Response to Reviewers
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Title: Evaluating Adverse Drug Event Reports in Administrative Data of Emergency Department Patients: A Validation Study
Review 2

Dear Dr. Jones,

We thank you and your reviewer’s thoughtful comments on our paper. We have revised the manuscript according their comments, and have responded to their concerns below (in blue). We list the reviewer comments in the order of their appearance.

Please note that what used to be Appendix C has become Appendix B in this revision.

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 (Zed): No edits requested.

Referee 1 (Budnitz):

1. The case definition and use of the term “adverse drug event” remains problematic. The authors make a case to use the more broadly construed IOM definition of adverse drug events (ADEs) and cite Nebeker et al. in their rationale. They also have added Appendix C to better define the types of ADEs. However, even if a broadened definition that includes harm from dose reductions and discontinuation is used, additional events that are included in the case definition remain problematic, such as the following:

   -- All of the cases classified as “Need to Add a Drug/Untreated Indication” (16%) probably should be excluded. These are all situations where a drug was never considered to be used in the first place. As noted by Nebeker “[t]he term adverse drug event does not include failure to use a drug in the first place, which is not a use of a drug.”
   -- The category “Failure to Receive Drug/Noncompliance” includes definitions in which the implicated drug is not used in the first place (e.g., “Not taking a drug as directed because it’s not consistent with the patient’s health belief” or “Drug not available”).
   -- The category “Drug use without indication” comprises only 2% of cases but according to Appendix C, it includes “Recreational use”, “Alcohol abuse”, and “Addiction/dependence”. Are the authors implying that every ED visit involving harm related to abuse of a pharmaceutical substance or alcohol is an ADE? Presumably not, else many more cases would be included.

   Thank you for the opportunity to clarify. We applied the taxonomy presented in Appendix B (previously Appendix C) only after the case definition of an adverse drug event was met. Therefore, some of the situations listed in Appendix B were not present in our study. For example, there were no cases that were “at risk of developing a new medical condition and would benefit from prophylactic drug therapy”, as no such cases would have met our case definition of an adverse drug event as all cases had to be associated with an emergency department visit, and had to present with untoward and unintended symptoms, signs or abnormal laboratory values. To address the reviewer’s comment, we have edited Appendix B from its original presentation, and have omitted those categories that were not possible in our study.

   Cases in which drugs were never considered for use in the first place were not considered adverse drug events in our study. To categorize the event as “Need to add a drug/untreated indication” or “Failure to receive drug/noncompliance”, a pre-existing diagnosis had to have been established before the emergency department visit. An example in this category is a patient who presented to the emergency department with one seizure who seized a second time while in the department. This patient had previously documented seizures that had been well controlled on anti-epileptics before the patient decided to discontinue the medication. We searched for previously established diagnoses and previously dispensed medications using our regional electronic medical records, the paper-based chart and the provincial electronic drug dispensing database for a 12-month period retroactive from the date of the emergency department visit. To address the reviewer’s comment we have clarified the requirement of a previously established diagnosis in these categories in Appendix B.

   In this study, we only considered adverse drug events from medications, not from any alcohol-related events, or any events related to illicit or recreational drugs. We have removed these categorizations from Appendix B to clarify. We would only have included “addiction/dependence” to a medication, if it resulted in an adverse event prompting an emergency department presentation (i.e., acute narcotic withdrawal symptoms for which the patient sought emergency department treatment, in a patient...
dependent on prescribed narcotics). Addiction/dependence per se (without being associated with an emergency department visit) was not considered an adverse drug event. In our case series we did not encounter any events related to this categorization.

Thank you again for pointing out these nuances above. We believe that clarifying these is critical to the clarity of our manuscript. We have edited Appendix B and the Methods section under “Identification of Adverse Drug Events at the Point-of-care” and “Definitions”.

2. In their response to the editor, the authors explain why the number of ADEs reported in this manuscript (221) is different than the number reported in a previous publication based on the same cohort (131). Apparently, in their previous paper using the same cohort to describe a clinical decision rule for ADEs they did not consider “need to add a drug” and other additional situations to be within the definition of ADEs; but for this manuscript assessing the validity of using administrative data for identifying ADEs they decided to use a broader definition in which they did include “need to add a drug” and other situations as ADEs. For the same authors to use the same cohort and the same term (ADE) but change the definition without directly explaining in the manuscript is problematic. We have edited the manuscript to describe the difference between the manuscripts (See Discussion section, page 19).

3. The authors do address the issue of a broadened definition of “ADE” in the discussion, and examples of ”Need to Add a Drug/Untreated Indication” are very much appreciated (pg 18-19). However, these examples raise the question of where such a broad definition of ADEs ends. To consider all patients in DKA and all patients with ischemic strokes to be instances of ADEs is taking the definition of an ADE to such an extreme that the term ADE approaches meaninglessness. Is any disease progression that might have been altered by adding a medication an ADE? In the primary care setting, is every patient with high cholesterol or hypertension suffering from an ADE due to an unmet “need to add a drug” (a statin or an antihypertensive)? Is every patient who uses tobacco or is obese suffering from an ADE because they might conceivably be treated with a pharmacologic therapy to wean them off nicotine or to suppress their appetite? The authors might argue that hypertension or obesity is not a "harm" or an "injury" but really this is just a matter of disease severity or disease progression. Obviously death is the most serious injury, so is every suicide by a patient with depression an ADE because the patient was not treated with adequate antidepressants? The authors should address the implications of the "slippery slope" of broadening this definition as well as specifically how policy makers, clinicians, and patients would use such a broad definition for specific interventions.

We agree with the reviewer that the definition of “harm” and “injury” are ambiguous and that too broad of a definition of adverse drug events is problematic. We approached our case definition of adverse drug events from the health services research perspective, in which the utilization of the emergency department leading to bed occupancy and cost, was the primary end point of interest. Thus, all our cases were associated with an emergency department visit, and we did not capture any “harm” or “injury” from illnesses not associated with an emergency department visit.

We excluded cases deemed possibly due to the exacerbation of underlying disease using three mechanisms: (1) In the pharmacists assessments we mandated the use the Naranjo algorithm which makes the diagnosis of an adverse drug event highly unlikely (leading to the subtraction of 2 points on a 10-point scale, making it virtually impossible to accumulate sufficient points to be considered an adverse drug event). (2) We collected data on the working diagnosis of treating physicians via face-to-face interviews to ensure that we understood the physician’s working diagnosis as a means of ruling out
other diagnoses, including exacerbation of underlying disease. (3) In our adjudication process we used the Forster algorithm, which asks the raters whether the symptom was more likely due to treatment or the underlying disease.

To address the reviewer’s comment, we have edited our discussion (Pages 18 and 19) section to highlight the health services research perspective we used to define adverse drug events, and to address the negative implications that a broader case definition of adverse drug events might have.

References