Reviewer's report

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

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Reviewer: Daniel Budnitz

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Major Compulsory Revisions
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 categorized 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.

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 other 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.
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.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests