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:
The case definition remains problematic and potentially misleading to readers; however, the acknowledgement in the Discussion section that the full case definition includes types of events that “may not be relevant from a pharmacovigilance or regulatory body perspective” such as “untreated indication,” “inappropriate dosing,” or “noncompliance” is recognized.

Nonetheless, as the authors continue to include these broadly construed ADEs, they should at least clearly state the percentage of the total ADEs that involve these types of events. This percentage appears to be approximately 60-66% of the total ADEs in the study (from Table 3), which would be quite important to note.

However, it is hard for a reader to determine this precise percentage because of inconsistencies in terminology used in the discussion text, in Table 3, and Appendix B. Please apply the same terms consistently throughout.

Specifically:
- Is “inappropriate dosing” mentioned in the discussion inclusive of “high dose” and “low dose” mentioned in table 3?
- Is “untreated indication” mentioned in the discussion the same as “drug use without indication” identified in the table or does it also include “need to add a drug”?
- “Need to add a drug” and “Untreated indication” are two separate categories in Table 3 but these two types are combined in Appendix B. Why? The authors should add “need to add a drug” to the types of events enumerated in the discussion text that may not be relevant from a pharmacovigilance or regulatory body perspective.
- Should “wrong drug” also be considered an ADE that may not be relevant from a pharmacovigilence or regulatory body perspective?

2. In the Discussion, the authors assert that they "believe" that monitoring a broadly construed definition of ADEs “is desirable in order to guide the development and evaluation of evidence-informed health policies to reduce their occurrence” but do not explain how coming up with a composite, broadly construed ADE measurement would be useful to inform health policies or reduce occurrence. Please do so.
The examples given by the authors -- a patient with high CHADS2 scores that did not receive anticoagulation, a patient whose furosemide dose is reduced and then has pulmonary edema, and a patient who was non-compliant with insulin and went into DKA – may be issues of potentially problematic health care (or may be the result of patient preferences or each may have its own web of complex causes), but the authors should explain specifically how labeling these disparate events “ADEs” is helpful for developing informed policies.

Identifying frequency of occurrence of each situation individually would be important for prioritization. Examining the underlying causes of each situation individually identify may guide specific prevention policies for anticoagulation, heart failure or diabetes management. But unless there is a common thread (e.g., lack of drug coverage led to the failure to use anticoagulants, led to lowering the dose of furosemide, and led to non-compliance with insulin) it is not obvious how lumping these situations under a common term, ADEs, helps inform prevention policies, unless it is a generic call that all health care providers should do a better job of high-quality prescribing and all patients should be more adherent to prescribed medication regimens.

Discretionary Revisions:
3. Table 5 assesses the specificity of ICD code identification of ADEs (True Positive Cases identified by ICD codes / All True Positive Cases), but no mention is made of False Positives. Could a False Positive rate be calculated? The False Positive rate is particularly important for the broader ICD codes. For example, to identify the 62 of 221 ADE cases using the broader ICD codes, how many cases of the total cohort were flagged by broad ICD codes as potentially having ADEs but did not by gold standard chart assessment. Did the ICD codes only identify these 62 cases or did they identify 500 of the 1574 patients (in this example 448 False Positives). If ICD codes were to be used to identify ADEs this would be very useful information and a high False Positive rate is further evidence that ICD coding may not be up to the task of identifying ADEs.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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