Reviewer's report

Title: Comparison of Pharmacy-Based Measures of Medication Adherence

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Reviewer: John Zeber

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General Comments:

While a very interesting topic and well-intentioned study, I personally found the presented very complex, confusing, and with an unclear set of implications for either clinical care or advancing the research agenda. This perspective started with the abstract, an introduction that did not provide a sufficient review of the issues and prior work, and a lengthy but overly dense methods section. While I support many of the discussion points, I am unconvinced much of the audience will be able to utilize the significant amount of work comprising the analysis, as the description and overall presentation presents a challenge. Yet understanding the challenges of using pharmacy date and its limitations, I do encourage revision efforts to elucidate the issues raised here.

Specific Comments: major

1. abstract: a little clarification here is needed re: what measures require “dispensing to be calculated” vs those that do not – consider providing a short example of each; this lack of definition is only clarified later in the text, plus some information in table 2. I am also confused and disagree with the statement that administrative pharmacy data measures cannot be defined well for large populations. Instead, such approaches are frequently used in population studies of large healthcare cohorts using administrative pharmacy databases. This includes, from what I understood, your own study.

2. one major problem I experienced with understanding this study was the fact that, in my copy, the Methods section followed the discussion. This is perhaps an issue with uploading the file, but admittedly colored my initial perspective and led to some confusion.

3. not sure I agree there is little published information on comparing pharmacy measures, and would suggest citing 1-2 papers that used a few of your 8 measures (MPR / PDC is frequently used, with increasing work on gaps in general), whether validated against some objective outcome. A summary of noted strengths and weaknesses of these approaches would be useful to the reader as well; as noted below, much of the detailed Methods might be cut to allow room for such information. Otherwise, simply presenting a detailed review on measure construction, even with the practical RCT example, seems to push this paper towards being quite theoretical and not sure it could significantly improve upon past pharmacy research.


4. contributing to a more theoretical (and naturally methodological) appearance of this paper, the Methods section is very long and complex in describing the different measures. Though I am perhaps misreading the journal audience, I suggest moving much of the detailed information, including the measure formulas, to an appendix (with article or online supplement). Another option is presenting all 8 measures in a flow chart format, listing the variables for time (t), dispensing length (n) and so forth in a more visual, graphical manner. The same would work for continuous and gap measures.

5. how did the authors, using any of the measures (though more important for continuous ones rather than gaps), account for inpatient lengths of stay? This can be an issue since long admissions reduce the likelihood of outpatient pharmacy days covered, and is therefore often addressed in MPR/PDC type studies.

6. to be honest, despite several runs through the analysis section, I am not sure what information Table 2 presents, and the Results text does not clarify it well. It would appear that the means represent MPR equivalents, but not sure what percentiles indicate. “Upward bias” is also perhaps a slightly inaccurate term without defining what a gold standard of accurate adherence measurement should be.

7. so 1/3 of these patients only had 1 fill (as suggested by 3 of the measures), and 17% never had a prescription? Most studies would exclude the latter patients completely. Again, it is still not clear at this point what “needs dispensings to calculate …”

8. perhaps equally important from a research perspective, as noted by the authors, one major problem with any adherence study is not knowing truly when a patient was prescribed a medication, when they truly stooped taking it during a defined period, not to mention the actual adherence behavior of taking filled
prescriptions. All, this uncertainty often overwhelms the distinctions between measurement approaches and “bias”.

9. these significant concerns (or at least confusions regarding the approach) aside, such examinations are important as adherence research continues to evolve, along with how such research relates to improving clinical care and monitoring must be further addressed in the literature. The Discussion section is well written, the clearest of all parts of this paper, and does indeed cover the most salient issues. However, it is also long and wanders through a variety of points related to the 8 measures. Although some key points are summarized nicely (e.g., window length important, need to understand what we are measuring), I am having difficulty seeing the overall utility and application of these findings to either research or clinical practice. Granted, much of this might be attributable to my lack of complete understanding of the specific methods.

Other suggested discretionary or other comments:

1. further support of the study significance might be made concerning the of pharmacy databases is increasingly essential in examining adherence issues in large health care systems (HMOs, VA, Medicaid and Medicare, etc.). The first part of the introduction addresses some of this, but most pharmacoepidemiological research absolutely depends of such databases and systematic adherence measures.

2. save any commentary about the findings until the Discussion; e.g., early in the Results the authors note “two points are worth noting”.

3. given the length of this paper, not sure how much detail is needed regarding the RCT and intervention itself, since the primary objective is the adherence measures, though some detail is helpful for context.

4. I strongly suggest adherence not be capped at 1.0 for any study – our own work and that of others have demonstrated that patients with very high values are a special subset of sicker or more unstable individuals that need to be monitored carefully (i.e., values above 1.0 are important to capture).

minor points: [all minor, perhaps subject to journal’s formatting requirements]
1. check for comma used following e.g., / i.e.,

Level of interest: An article of limited interest

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.