Reviewer's report

Title: Comparison of Pharmacy-Based Measures of Medication Adherence

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Reviewer: John F Steiner

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Measures of refill adherence are increasingly used clinically, in comparative effectiveness and pharmacoepidemiological studies to assess drug exposures, and to assess quality of care. The decision of the Medicare program to use these measures as part of the quality measurement program for its Medicare Advantage plans makes this investigation of alternative methods of assessing refill adherence even more relevant. Strengths of this paper include its clear description of alternative measures (in formulas, in words, and in the helpful Table 1), its description of the relationship of these measures to prior literature, its balanced illustration of the tradeoffs between these measures in estimating adherence, and its demonstration of the dependency of several of these measures on the period of observation. The authors emphasize the important point that adherence measures (and adherence itself) typically decline over time – a covariate that is often ignored in papers in this field. In particular, CMA7 and CMA8 are novel measures, and while their applicability may be limited (as the authors note), these are creative additions to the set of possible adherence metrics.

Major compulsory revisions: None

Minor essential revisions:
1. Unless required by the journal, the methods section currently follows the conclusion, and should be moved to its usual location.
2. Refill measures are usually calculated for pills rather than inhalers. Additional description in the methods section about the adaptation of these measures for use with inhalers would be useful to readers who are unfamiliar with this variation on the standard approach.
3. Table 1 is a nice summary of the differences between measures, but the column labeled “timing” in the table probably requires more description as a table footnote so that the table can stand alone.

Discretionary revisions:
4. While the authors are correct that many researchers cap these measures at 1.0 (p. 14), their statement that there is no theoretical reason why adherence can’t be > 1.0 is incorrect, and in fact they provide theoretical arguments for not truncating these measures on p. 7. Patients can certainly take an excessive number of inhalations; while this is less often a problem for inhaled corticosteroids, it has been a notorious probably with beta-agonist inhalers. Thus,
the authors might provide a more critical assessment of measures CMA3 and CMA4, which may obscure important information in some circumstances. Their conclusion that CMA1 and CMA2 should not be used simply because researchers don’t generally consider the problem of “overadherence” seems like a weak argument given their own recognition of reasons why adherence >1 should not be ignored.

5. The decline in adherence over time can be interpreted in two ways. The authors define it as a source of bias, which is true if duration of observation is ignored in an analysis. However it may also be a valid measure of a change in the underlying behavior. The authors should note this in order to avoid conveying the impression that reduction of bias is the only rationale for prolonged observation of refill behavior.

6. At the top of p. 7, the authors distinguish between medication acquisition and “true adherence”. It would be more precise to use the term “medication-taking” rather than “true adherence”. Refill adherence measures are a highly valid measure of one behavior – obtaining refills from a pharmacy - and an imperfect measure of medication taking, but both are “true” behaviors.

7. In the last 2-3 years, several papers have reported that a high proportion of patients never obtain the first fill of a medication ordered by their clinician. Since the authors so carefully identify other sources of bias in these common measures of refill adherence, the bias inherent in requiring even a single fill of a medication probably deserves at least brief mention in their discussion.

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 am an employee of Kaiser Permanente, but am not engaged in research with any of the authors of this paper.