Reviewer’s report

Title: Proton Pump Inhibitors and the risk of pneumonia: a comparison of cohort and self-controlled case series designs

Version: 2 Date: 6 September 2012

Reviewer: Jessica Myers

Reviewer’s report:

Major essential revisions

This paper provides a comparison of new-user cohort and self-controlled designs in the example of PPIs and acute pneumonia. The example chosen is appropriate for this comparison, and the comparison is potentially interesting.

The primary criticism of the manuscript in its current form is that the methods are extremely difficult to follow. The description of what was done in each of the two designs is vague. Given that the entire point of the manuscript is to compare the designs, it is of utmost importance that the designs be well understood and that details of the design be stated explicitly.

For example...

p.5: In the cohort study, what is the comparator group? Is it really all patients unexposed to PPIs? If so, for the unexposed, what is the date of entry into the cohort?

p.5: What is the purpose of excluding patients that received H2RA in 6 months prior? One sentence on the clinical reasoning would be helpful to methods-oriented investigators that may read this paper.

p.5: What is the purpose of the exposure duration interval? How was it used in the two designs? You don’t state that end of exposure interval is a reason to censor in the cohort study, so does that mean that the exposure duration was only used in the self-controlled study?

p.6: What is meant by “clustering of patients”? Do you mean clustering of observations within patients? What is the hierarchy that is used for the GEE model?

p.7: In the cohort study, when were covariates assessed? For example, use of tiotropium – is this any use during the study or use prior to exposure?

p.8: What are residual time periods? Does that mean any time with available data either before or after exposure (excluding the specific time periods indicated)?

p.8: Why not use GEE for the self-controlled model? Are there again multiple observations per patient?
The second important criticism of the manuscript is that it lacks sufficient discussion of the results to make the study really useful and informative. For example, in both designs, there are major differences between the 1-7 day rate ratio observed and what was seen in prior observational studies. The authors do not mention this difference, but some discussion would be helpful. Also, by far the largest association was observed prior to exposure in the self-controlled design. Does this clearly non-causal association have implications for their assumption of causality in the post-exposure periods?

Minor essential revisions

p.3: It is not possible to control “more adequately.” Control is either adequate or inadequate. Also, should be more specific about what is meant by “constant” patient specific confounders. I assume you mean non-time-varying.

p.3: The description of confounding by indication in the self-controlled designs at the bottom of this page is hard to follow.

p.9: The stratification happens at points specified a priori.

p.9: The last phrase of the first discussion paragraph is not a sentence.

Discretionary revisions

Understanding of the methods could be greatly improved with the inclusion of diagrams that depict the timeline of exposure and follow-up in each design.

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.