Reviewer’s report

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

Version: 3 Date: 9 January 2013

Reviewer: Michele Jonsson Funk

Reviewer’s report:

Thank you for the opportunity to provide additional feedback on this manuscript. It is greatly improved, and the authors have been responsive to the questions raised in my initial review.

Major Compulsory Revisions

1. The authors state in the discussion that “our sensitivity analyses showed that adjusting for potential time-varying confounders made little difference to the risk estimates in the self-controlled case series design suggesting the method is robust to unmeasured confounders”. While I think it is fair to claim that the potential bias due to residual confounding by these time-varying factors was limited, I don’t think one can conclude on the basis of a single result that this method is robust to unmeasured confounders. I would suggest striking the underlined portion of the sentence.

2. The sensitivity analysis of the SCCS limited to those patients who were alive at discharge was informative. Given that the primary estimates for the RR in the 1-7 days post-exposure are 22% higher than those obtained after limiting the sample to patients who were alive at discharge, I think the numeric results of this sensitivity should be included. As a methods paper, this is also an opportunity for the authors to highlight this issue and discuss how it can be dealt with rather than simply reassuring the reader that it is nothing to be worried about in this specific analysis.

3. Please report the characteristics of the populations (person-time) stratified by exposure group. As presented now, Table 1 does not allow the reader to assess the extent to which confounding is likely to be a concern. Characterizing person-time (rather than people) stratified by exposure status (in both the cohort and SCCS designs) will allow the authors to report the distributions of time-varying characteristics which were included in the adjusted analysis, but are not presented included in Table 1.

4. The authors have not adequately addressed item #6 in my original review which dealt with re-classifying exposed person-time during the grace period after an initial record of dispensed PPI. This is an issue of re-classifying a portion of ‘exposed’ person-time as unexposed if, and only if, the patient survived to the end of 3 intervals without an additional dispensing. If day 0 is the index date when the PPI was dispensed, then defining exposure for days 36 through 108
based on information (no additional dispensed PPIs through day 108) that is not known until day 108 is problematic since this can only be done for those individuals who remain alive at the end of that period of time. I believe the appropriate method for dealing with this is to allow a grace period (if desired) but then only change the classification of person-time from exposed to unexposed at the end of the grace period. If I have misunderstood, please clarify-

Discretionary Revisions
1. The results provided in the response to reviewers which included the RR for the new pre-exposure period (61-120 days) were helpful. I suspect that the risk is still elevated in the early portion of this period (perhaps 61-90 days), and near the ‘true’ background rate toward the end of it. I think it would be helpful to include the numeric results in the text, but I leave it to the authors to decide if excluding the pre-exposure period from 61-90 days (for instance) would strengthen their findings.

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:
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