Reviewer's report

Title: A Retrospective, Matched Cohort Study of Potential Drug-Drug Interaction Prevalence and Opioid Utilization in a Diabetic Peripheral Neuropathy Population Initiated on Pregabalin or Duloxetine

Version: 3

Date: 11 July 2014

Reviewer: Andrew McLachlan

Reviewer's report:

GENERAL COMMENTS

This manuscript reports on an observational study using pharmacy claim data that investigates the co-prescription of potentially interacting medicines with 2 commonly used medicines in the setting of painful diabetic peripheral neuropathy (pregabalin and duloxetine) and the impact of this on healthcare cost and utilization and the use of opioid analgesics.

The premise for this study is a little unclear. Given the nature of the clinical pharmacology of pregabalin (predominately renally excreted) and duloxetine (CYP1A2 and CYP2D6 mediated metabolism) it is clear (and even well documented) that pregabalin has a considerably lower potential for drug-drug interactions than duloxetine. This is reflected in the number of people who were identified as taking potential DDIs in the pregabalin group (3%) and duloxetine (57%). These data align with other studies.

This manuscripts cites a paper by Johnson et al (reference 28 in the manuscript) which conducted a very similar study in the exactly the same cohort of patients (diabetic peripheral neuropathy) investigating drug-drug interactions and drug-disease interactions. The differences is that Johnson et al paper used claims data from 2499 pregabalin users and 1354 duloxetine users whereas the study described in this manuscript involved considerably less people (466 in each group).

The strength of this manuscript is the authors attempt to understand the impact of potential DDI. Co-prescription implies comorbidity – which in turn can contribute to increased health care utilization and costs. In this study the authors accounted for this using a clinical comorbidity index derived administrative data.

The limitation is the very limited data in the pregabalin group which prevents meaningful analyses.

SPECIFIC COMMENTS

1. The authors have focused on one clinical indication (painful diabetic peripheral neuropathy) for pregabalin and duloxetine using ICD-9 codes for this condition. Is it possible that the findings of this research could be generalized to other indications such as neuropathic pain (which is a more common indication for these medicines)?
2. The authors have derived the potential drug interactions for pregabalin and duloxetine from Micomedex yet these are not listed in this manuscript. A table outlining the potential interactions that were investigated and details of which “potential DDIs” were actually found in the cohort would be most useful for the reader. Which potential DDI combinations were more common?

3. Were potential pharmacodynamic drug interactions also investigated (eg serotonin interactions for duloxetine and concomitant sedatives for pregabalin)?

4. The rationale for investigating the utilization of opioid analgesics in the context of potential DDIs is unclear and needs further development/justification in the present manuscript. This seems to focus on claims of opioid sparing effects of pregabalin when compared to duloxetine, however the link to potential DDIs is unclear to this reader.

5. Provide a clear commentary on the novel aspects of this research over and above the findings of the paper by Johnson et al (reference 28)

6. A key challenge with this analysis is the very small number of potential drug-drug interactions with pregabalin – this limits the ability to make valid and insightful observations especially in comparison to duloxetine

7. The authors make the important observation in the Discussion that “Causal effect cannot be assigned” yet the tone of the conclusions and other parts of this manuscript imply that this study provide evidence that pregabalin is a better choice than pregabalin. Can the authors directly attribute the slight increase in healthcare costs to potential DDIs with duloxetine (as implied from the conclusions)?

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

None to declare