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

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Reviewer: Kenneth Candido

Reviewer's report:

1. Is the question posed by the authors well defined?
Yes, the question posed by the authors is well defined. They are comparing the potential for drug-to-drug interaction prevalence and use of opioids in individuals treated with either Pregabalin or Duloxetine used for managing pain associated with diabetic peripheral neuropathy (DPN). This is well defined and clearly established and the paper does a nice job of remaining focused on these tasks for the Methodology and Conclusion sections of the report.

2. Are the methods appropriate and well described?
Yes, the Methods are appropriate and are well designed and described.

3. Are the data sound?
Yes, the Data appear to be consistent with the Methodologies utilized in the present case to determine statistical significance in drug-to-drug potential interactions as well as opioid utilization in these patients. Using standard database searches, the authors have assessed prescription claims over a prolonged period of time (48 months). The aggregate number of subjects is robust (446 in each group). Of course, one would expect there to be a finding of increased potential DDIs with Duloxetine due to its dual nature of action (serotonin and norepinephrine reuptake inhibition) and the multitude of warnings mandated by the FDA during the review process of the NDA for this agent for treating, in addition to depression, neuropathic pain and musculoskeletal type pain. The key word is “potential” as this does not correspond to actual reporting data for an actual incidence of adverse events when either Duloxetine or Pregabalin are presently used in approved clinical conditions and in approved dosing regimens.

Furthermore, the opioid data did not demonstrate a statistically significant finding in favor of one of these agents over the other in terms of providing opioid-sparing effects. This is an important consideration when evaluating the data, which was pointed out by the authors.

4. Do the figures appear to be genuine, i.e. without evidence of manipulation?
Yes the figures do appear to be genuine and without evidence of manipulation.

5. Does the manuscript adhere to the relevant standards for reporting and data
deposition?
Yes the manuscript does adhere to the relevant standards for reporting and data deposition.

6. Are the discussion and conclusions well balanced and adequately supported by the data?
Once again, we are discussing a mere proposition of a “potential” for DDI; there is nothing actually proven by these analyses. The fact that a drug appears to have a potential for a drug-to-drug interaction with other chronically consumed medications does not translate to actual adverse events of such an interaction occurring. Many examples of these types of potential DDIs exist for which there is more of a theoretical concern than a practical concern. The present paper is more of a study of the economics of utilizing two distinct chemical agents for managing DPN related pain, while it is not a study of the actual AEs that occur when these two drugs are given in conjunction with other chronically consumed medications. All data are retrospective, which further flavors the interpretation of any conclusions that can be drawn herein.

7. Are limitations of the work clearly stated?
Yes the limitations of the work are clearly stated.

8. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes the authors do clearly acknowledge any work upon which they are building.

9. Do the title and abstract accurately convey what has been found?
Yes the title and abstract both accurately convey what has been found.

10. Is the writing acceptable?
Yes the writing is excellent.

I have some suggestions regarding the interpretation of data collected retrospectively; among these is the insinuation that an "exposure to a potential DDI" led directly or indirectly to high mean total 6-month costs in chronic pain subjects. I agree with the authors that "...the statistically significant findings difficult to interpret in terms of clinical relevance". We simply do not know how a potential for a DDI could have contributed to these differences without having data to support any actual DDIs having been considered to source for outpatient medical visits or emergency room visits. Other confounding factors need to be considered or else possibly this entire section could be removed. Unless one undertakes an analysis of the registry of admission of every case included in this database, any conclusion as to the etiologies for these admissions or visits is purely speculative.

**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 declare that I have no competing interests.