Author's response to reviews

Title: Dose patterns in commercially insured subjects chronically exposed to opioids: a large cohort study in the United States

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Author's response to reviews: see over
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Miss
Colette Homan
The BioMed Central Editorial Team

Dear Miss Homan,

It is with great pleasure than we resubmit the manuscript: 1516687566303675 Dose patterns in commercially insured subjects chronically exposed to opioids: a large cohort study in the United States.

You will find below our responses to the reviewer’s and Editor comments. I hope that the Editorial Team and Editors find them satisfactory.

Sincerely,

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Response to Editor

(1) Document, within the methods section of your manuscript, whether the data used for your study is openly available. If, alternatively, you received ethics approval please document the name of the committee which granted this.

Response:
We moved the following phrase: “Access to the PharMetrics database requires a license agreement and the data are provided de-identified” from the end of the Background section to the Methods section as the Editor suggested and added “Tabulations from these data do not require ethics approval”.

Response to Reviewer

1. Restate the phrase in the abstract and discussion from "require" to something like "escalate to".

Response:
As the reviewer suggested we do not use “require”. The sentence in the Abstract and Discussion now reads: “Seven percent of subjects with no cancer diagnosis will be exposed to high doses of opioids at some point”

2. There should be text and references added to background section on the epidemic of deaths, and more discussion of the Dunn et al article on the relationship between dose and morbidity/mortality. Looking at the P95 doses in both the intermittent and continuous groups, what number of cases in this commercially insured population could be at risk—that is, how many are on at least 100 mg/day MED?

Response:
As the reviewer suggested we now report the percentage of subjects who at any moment were exposed to 100 mg or more of morphine in the intermittent and continuous groups and the rationale for doing so. We also now discuss in the Discussion section these results and the potential implications of receiving such doses and cite the Dunn paper as requested.

3. There should be reference to and discussion of another recently published study that did demonstrate important dose escalation within one year in a workers’ compensation population with low back injuries (Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic back pain: A prospective, population-based study among injured workers in Washington State, 2002-2005. Clin J Pain 25:743-751,2009). The authors refer several times in the manuscript to high doses being associated with severity. While this is probably true in general, the study just cited reported substantial dose escalation in the absence of clinically important improvement in pain and function. Along these lines, what one would want to know, along the lines of the other reviewers comments, is what happens to dose in a stable cohort on longer term opioids. So, for patients who remain in this system on continuous opioids over several years, what happens to their dose.

Response:
As the reviewer suggested we have added the reference and we have added a paragraph in the Discussion section that describes the results of the study by Franklin et al.

4. The 95th percentile dose in the continuous group is high (141) even in the first half-year, and this dose increases rather dramatically in the first 2 years. Again, the authors are not paying due attention to the tail—it is likely these patients at greatest risk of substantial morbidity and mortality. ‘Even in the intermittent group, the P95 is quite high (112): how many patients does that actually represent in this larger group?

**Response:**
As the reviewer suggested, we have added the percentage of subjects who at any moment reached doses of 100 mg or more of morphine equivalent and have added to the discussion the implications of the findings.

5. The authors have not spoken clearly enough to the possible limitations of their included population in studying this question. In the intermittent population, included patients could have had no more than several doses per year, perhaps with surgical procedures, for acute injuries, etc. Also, the index dose could have been a strong opioid, but the second dose could have been a weak opioid.

**Response:**
We agree with the reviewer that the intermittent exposed group includes subjects with subacute pain, pain exacerbations and chronic pain. We do not see this as a shortcoming. Health care providers are interested to know the opioid dose pattern in patients who are intermittently exposed to opioids. Nonetheless, we have added to the Discussion that the intermittent group potentially includes subjects with subacute pain, pain exacerbations and chronic pain.

6. Page 6—the authors mention that specific dispensing data for an individual could have been missing but the subject’s doses still included in the analysis. What proportion of such cases were included? How would this have affected the median and average doses reported? Why was specific dosing missing—is this a data entry problem at the insurer level?

**Response:**
While doing the analysis to quantify the number of subjects and prescriptions with missing daily dose we realized that none of the subjects that remained in the analysis after the initial exclusion step had missing daily dose data. We deleted that statement in the current version of the manuscript.

The initial exclusion step is described in the Results section: “8,362 (14%) subjects were excluded because of missing data on the quantity dispensed or the days supplied, leaving 48,986 subjects whose dosage patterns were examined in the present study”.

7. I would like to see Table 4, reported as it is, broken down by cancer and non-cancer. You can delete Table 6 with the added information in new Table 4. And additional discussion added for new Table 4 depending on what you find

**Response:**
As the reviewer suggested we now report the results by presence or absence or cancer diagnosis.
8. Page 8-report the median, average and range of dosings

Response:  
As the reviewer suggested we added the dose values to each of the measures we listed in the paragraphs, mean, median and 25th, 75th and 95th percentiles.

Minor essential revisions
1. Page 3, 2nd paragraph-you sought to characterize the dose of opioids in patients intermittently and chronically exposed to opioids, in both cancer and non-cancer patients.

Response:  
As the reviewer suggested we now stat “We sought to characterize the dose of opioids in both cancer and noncancer patients intermittently and chronically exposed to opioids”