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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Natalie Pafitis, MSc
The BioMed Central Editorial Team

Dear Ms Pafitis,

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

You will find below our responses to each one of the reviewers’ comments. I hope that the Editorial Team and Editors find them satisfactory.

Sincerely,

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Response to Reviewer: Mark Edlund

I did have two questions that need to be clarified.
(1) Just to be clear, are “strong” opioids those opioids in table 1? Or those in table 2? It must be those in table 2, as clearly buprenorphine does not meet the criteria, and it does not seem like tramadol would either.

Response:
The reviewer is correct. To avoid confusion, in the current version of the manuscript we now introduce what was Table 2 earlier in the manuscript. Consequently Table 2 is now Table 1. We also rename it and cite the “new” Table 1 when describing the medications considered strong opioids.

(2) How was it known whether patients were receiving opioids for treatment of opioid addiction? That is, if a patient was on methadone, how was it known whether the methadone was for pain or addiction? However, this is a relatively minor issue, as so few were on methadone. However, my major concern is with the set up of the study, and interpretation of the data.

Response:
Pharmetrics has information on medical conditions. We used ICD-9 codes for drug abuse or drug dependence. Any subject with any of these ICD-9 codes was excluded. We have added this information to the current version of the manuscript in the subsection “Inclusion and exclusion criteria”.

(3) High utilizers of opioids tend to be a fairly small group, and by focusing on measures such as the median, mean, P25, and P75, do we adequately capture what is happening? For example, it might be interesting to see what happened in the 95th percentile.

Response:
As the reviewer suggested we have added to the analysis the 95th percentile.

(4) In the strictest sense, this type of analysis does not actually investigate dose escalation in individuals. Consider the simple example where there are just two individuals—each at 100 mg morphine dose. Say in the next period one individual increases his/her use to 180 mg, and the other decreases to 20 mg. In this case, with this type of analysis we would say there was no dose escalation, but really what happened was there was both dose escalation and dose reduction. Thus, the author’s analysis focuses on dose escalation in the group, but really does not get at dose escalation in individuals. Is there a way the authors could look at this? For example, I think the study would be much more informative if it looked at the percentage of individuals whose dose was 50% higher after one year, or 50% higher after two years (just an example).
Response:
We agree with the reviewer that average (mean or median) dose does not provide a full description of dose patterns. This is the reason for calculating the percentage of subjects who were exposed to 180 mg or more or 300 mg or more of morphine-equivalent at anytime. These analyses provide the information that the reviewer would like to see - dose in individuals. In the example that the reviewer provides, our analysis will conclude that 50% of the subjects will increase the dose. No changes were made to the manuscript.

(5) I think the authors are over-optimistic in how they characterize their conclusions. For example, they write in the abstract “Dose escalation is also uncommon in the first 2 years of continuous exposure to opioids, especially in those subjects with non-malignant conditions.” However, the mean dose among all patients did increase from 63 to 78, a 24% increase, in the first two years. Further, the abstract does not mention that in those with continuous exposure, after 4 years the mean has more than doubled, as has the P75—although this is dealt with in the text. Thus, the data could be “ spun” a different way. Similarly, the authors write “the low proportion of subjects who required very high doses of opioids confirmed that large dose escalation is a relatively uncommon phenomenon”. However, 7.6% of individuals of continuous opioids patients were at some point on a dose greater than 180 mg—some might characterize this as a low proportion, others might not.

Response:
As the reviewer suggested we have modified the current version of the manuscript and now avoid any subjective description of the findings in the abstract or in the main text. We also have added the size of the dose increase to the conclusion in the abstract.
Response to Reviewer: Gary Franklin

1. The "participants" presumably only include those who have continuous coverage by a commercial insurer through employment; as such, anyone who leaves employment related to pain-related disability would likely not be included here. For example, besides the Medicaid population, this data source would exclude thousands of injured workers treated for chronic pain through workers' compensation insurance. The study source used here would also exclude the large number of employed uninsured persons. As the authors intimate, the rather rapid fall off of numbers among the continuously followed cohort may represent the worst patients leaving the system for another method of coverage. Thus, this study may severely underestimate counts of those most likely to have disabling pain, and thus those most likely to actually develop problems with long term opioid use. These issues should be spelled out in much greater detail as limitations. In fact, the title would really most properly be, "Dose patterns in employed subjects..."

Response:

As the reviewer suggested we now state explicitly in the Discussion section that people with disabilities or injuries are under-represented and discuss the impact of these limitations on the study findings. See first paragraph, Page 14. We have modified the title as well.

2. The authors have defined the index case as at least 2 prescriptions of opioids within 6 months. But what one would really be interested in is the subpopulation which started out as an incident pain case, but then developed chronic pain. Chronic pain would be pain beyond 3 months. This is the principal population for which dose escalation is of substantial concern. Unfortunately, in the absence of indication information, this study cannot really clearly identify this important subpopulation. The methods used by Von Korff in the cited paper, as well as by Boudreau et al (Pharmacoepi Drug Safety 2009), should be repeated here to try to reproduce findings across studies.

Response:

We agree with the reviewer that it is the chronicity of opioid use that could lead to dose escalation. By requiring more than one opioid prescription we sought to exclude subjects who were taking opioids for acute episodes and focus on subjects with chronic pain.

We did have indication information. Similarly to Boudreau paper, we used ICD-9 diagnosis codes to identify pain indication information. We described pain indication in the first paragraph of the Results section.
We agree with the reviewer that this study and Boudreau’s study address chronic opioid use, but the aims of the studies are different. Boudreau et al study’s objective was to compare long-term use over time and the aim of the present study was to characterize opioid dosage over time therefore, we believe that the use of different methodologies is appropriate to these somewhat different aims. No changes were made to the manuscript.

3. There is no mention whatever in this manuscript of the studies related to substantial morbidity and mortality from unintentional poisoning by opioids; it is these findings that have led to the FDA REMS response, and to public health concern. The authors cannot conclude from the data analyzed here, and with the substantial limitations enumerated above, that “success of the adequate patient selection and careful evaluation by health care providers” can be construed from these findings. In fact, there is no evidence whatever that, beyond an initial history and physical, that any of the reasonable standards are being followed routinely. These would include routine urine drug monitoring, screening for past/current substance abuse, use of a treatment agreement, and tracking pain and function.

Response:
The aim of the study was to assess dose patterns and therefore we did not include morbidity and mortality from unintentional poisoning by opioids. We believe that it is important to encourage health care providers to follow guidelines when prescribing opioids because the aim of these guidelines is optimize opioid prescription. Although we did not delete the paragraph, we have added that patients receiving high doses of opioids are at increased risk of overdose.

4. There is mention of efficacy of opioids short term in the Introduction, but no mention of the paucity of data on lack of efficacy long term.

Response:
We modified the third paragraph of the Background section and no we state: "Little data exist to support the long-term efficacy of opioids or to describe the relation between opioid dose and the length of exposure among chronic opioid users".

5. The emphasis on median dose throughout is not really appropriate. It is likely that a smaller tail with inappropriate escalation is what is going on, but that is likely being missed here.

Response:
We have added to the analysis the 95th percentile and have included the results in the Results section and Discussion section.

6. What is the average dose over time of only the Schedule II longer acting opioids? These are likely the patients at the greatest risk for more dangerous escalation.
**Response:**
We did not plan to assess separately immediate or extended release opioid or examine separately those who used Schedule II opioids because confounding by indication could likely make the results of the comparison biased -- physicians are likely to prescribe extended release opioids preferentially to patients with more severe underlying disease. We made no changes to the manuscript.

7. What % of patients achieve doses of over 100 mg/day in each 6 month period? There is a paper in press that will demonstrate a 10 fold increase in risk of morbidity and mortality at that morphine equivalent dose.

**Response:**
According to the published literature at the time we did the study two cutoffs (180 mg and or 300 mg) thresholds that are commonly used to classify a subject as receiving high or very high doses of opioids. These cutoffs remain valid today. As the reviewer knows, predicting mortality from opioid doses is very challenging in observational studies because confounding by indication is a major problem. – Patients who receive high doses of opioid are likely to be more severely ill and therefore have a higher likelihood of dying and the Annals of Internal Medicine paper just published (2010; 152:85-92) concurs. To address the reviewer’s concern we have added to the Discussion section that subjects receiving high doses of opioids have an increased risk of overdose and need close supervision. We have added as a reference, the study that the reviewer referred to.

8. Who considers 50 mg to be a low dose? This is the average dose reported in several population-based studies. I would delete that statement.

**Response:**
As the reviewer suggested, we deleted the statement.