Reviewer's report

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

Version: 6 Date: 22 February 2010

Reviewer: Gary Franklin

Reviewer's report:

Major compulsory revisions

I have fully reviewed this paper once again, including the responses to the 2 reviewers. While the authors have made some changes and improvements in the manuscript, they have not been as responsive as would be prudent. They and everyone else realizes now that there is a public health emergency—an epidemic of death and morbidity associated with overuse of opioids for chronic, non-cancer pain. Their brief mention of the recent Dunn et al, 2010, publication does not do justice to the problem, since the authors continue to refer to doses of 180 and 360 as merely being high and very high, and refer to such doses in both the abstract and discussion as being "required". The Dunn et al study found a nearly 9-fold increased risk of morbidity or mortality at 100 mg MED. And as to "required", is severe tolerance "required"? Here are specific major compulsory revisions:

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

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?

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.
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?

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.

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?

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.

8. Page 8—report the median, average and range of dosings

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.

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 have no financial competing interests. I suppose one could say I have a non-financial competing interest in that I do not believe the author’s approach to the subject is as sound as it should be, and have published material that conflicts with their findings.