22-Sep-2017

Dear Dr. Brat

Manuscript ID BMJ.2017.040635 entitled "Post-Surgical Prescriptions for Opioid-Naïve Patients and the Association with Overdose and Abuse"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

dr. Wim Weber
European editor, The BMJ
wweber@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder(Chair), Julie Morris (Statistics advisor), Sophie Cook, José Merino, Rubin Minhas, George Rőggla, Tiago Villanueva, Wim Weber, Daoxin Yin.

Decision: Put points

Detailed comments from the meeting:

We thought your study addresses an interesting and potentially important research question. We had only a few queries:

You could stress that although the relative risks are significant, the absolute risk is very low.

Might you clarify the difference between abuse vs. misuse, and , if not substantial, limit to one of these terms ?

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
This is a timely study providing a new level of knowledge in an area that is lacking good quality data. The data provided in this article helps to clear out a lot of misconceptions in the area. It has real power to influence practice not only in the surgical field, but opioid prescribing in general. I congratulate the authors.

Overall the manuscript is well written. I have few specific comments.

General comments
In general, what do you mean by the term "misuse" and "abuse"? These terms have specific definitions. These terms are interchangeably used throughout the manuscript. I am guessing that these terms indicate a diagnosis of dependence, abuse or overdose. I would recommend changing the terminology and being consistent in using only one term, as it is a bit misleading and confusing in the current form. Something like "Problematic use" or "or opioid related problems" may be better. As authors pointed out, most overdoses are among short term users, not those who abuse, and "opioid abuse" is also just a subjective diagnostic code.

Introduction:
Para 2: "Surgeons play a large role in this epidemic by serving as a gateway to overprescribing medications that opioid diversion and epidemic"
This is a bit of a stretch. Surgeons prescribe a lot which can putatively increase opioid availability for diversion. But I don't think there is evidence that this contributed to opioid epidemic. The reasons for the opioid epidemic is much more complex than the often-reiterated statement that "doctors overprescribing caused the current opioid epidemic."

Methods: Solid, sensitivity analyses excellent.

Results:
Page 10: Several times the terminology "CP100K" is used. Provide the full expansion of the term "cases per 100,000" at least once in the results section for ease of reading. The authors have provided the full term in methods. Or they can use "case/100,000", CP100K is not intuitive.

Page 12, line 25: "For non-chronic opioid users, higher doses of opioids had smaller effects on the rate of misuse than additional weeks of exposure."
Please explain this. What do you mean by non-chronic or chronic user? Is this >90 days? I am guessing you mean >13 weeks.
eFigure 2 A and/or B are too important to be left in the appendix. Combined with figure 1 B, it demonstrates the persistence/worsening of "opioid related problems" despite the pendulum swing of number of prescriptions from 2008-2014 and stable dosage.
Page 11, line 51: "For both refills and duration, risk of misuse increased sharply at shorter periods and began to taper at higher levels of exposure (>11 weeks of duration)."
Is there data point connected to this statement? If so, please cite.
In additional risk factors of misuse, was a history of substance use other than tobacco available? This is an important factor. If not available or insignificant on analyses, please state that in results or discussion.

Discussion:
It would be comforting for surgeons and their patients to know that the rate of opioid related problems were small (0.2% in one year), but still significant because of the large numbers of surgeries done every year. So, I would encourage more forceful statement of that finding.

Page 14, second para: "Our data is consistent with several studies in surgical patients that have shown that early opioid administration after surgery is associated with subsequent long-term usage,(30, 31) a proxy for abuse."
A proxy for abuse here is a bit harsh given that only 0.2% develop abuse. Besides administering opioids just after surgery is necessary in many, but not without risks.
Please discuss the persistence/worsening of "opioid related problems" despite the pendulum swing of the number of prescriptions from 2008-2014 and stable dosage.

Additional Questions:
Please enter your name: Ajay Manhapra

Job Title: Lecturer, Department of Psychiatry

Institution: Yale School of Medicine USA

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Reviewer: 2

Recommendation:

Comments:
This is an interesting manuscript based on an Aetna database evaluating associations between post-operative opioid prescriptions and opioid misuse. They find a correlation between numbers of refills and duration of prescriptions in opioid naive post-surgical patients and the risk of opioid misuse. There are a number of minor issues in the manuscript including terribly difficult to read Tables and Figures (these should be trimmed in number if necessary for journal page length requirements but expanded in size those that remain). Methodology is also difficult to read at times (What is cabinet methodology?).

But in general the conclusions are largely impartial, nonopiophobic and data driven (with the exception of the phrase at the end of page 14 stating the "long-term usage is a proxy for abuse" - is this true for other medications they may be on long term after surgery?). However, there are three primary concerns I have with this manuscript which may or may not be due to a need for clarification only:
1) Do these data sets include discharge meds? or are all of the data outpatient meds which follow whatever prescription was given on discharge. If these discharge prescriptions were based on usual requirements it certainly puts the risks of one refill in a different light.
2) The opioid misuse characteristics includes quite a grab bag of diagnoses and one wonders whether who labelled the patients as having opioid dependence disorder. A physician frustrated at a patient's failure to get better despite multiple treatments including surgery? What happens when a smaller subset of opioid misuse outcomes (overdose?) are evaluated? At the very least this table of misuse diagnoses needs to be a NON-supplemental Table to make evaluation of the data easier for the reader.
3) Is it surprising to the authors given their conclusions that misuse numbers continued to rise despite the mean duration of exposure remaining stable (as described in the middle of page 12)? It is to me.
In short this is an interesting dive into a fertile dataset and if these confounds can be explained away or stated there are a number of interesting findings including the role of other pre-operative addictive disorders (tobacco and obesity) and pre-operative mood influencing comorbidities (chronic pain and depression) and the absence of risk for higher doses UNTIL several weeks into the post-operative period (where many epidemiologists might class them as chronic pain patients). I agree with the authors that for this reason this latter finding is certainly NOT in contradistinction to the chronic pain risk factor literature but an interesting supplement to it.

Additional Questions:
Please enter your name: Gregory Terman

Job Title: Professor of Anesthesiology and Pain Medicine

Institution: University of Washington; Seattle, Washington

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Reviewer: 3

Recommendation:

Comments:

Thank you for submitting this interesting article. I completely agree that there is a need to address acute care prescribing of opioids, and there are still a very limited number of studies addressing overdose and misuse after surgery. There are very limited data of misuse, abuse and overdose after acute care prescribing. The article is very well written, and the data collection and analyses (including multiple sensitivity analyses) were comprehensive.
Despite my enthusiasm for this work, I have some concerns and critiques that temper my enthusiasm.

Major critiques/overall comments:

1. Definition of misuse- My major concern is about the number of patients meeting the "misuse" criteria based on a diagnosis of "dependence." I worry that many clinicians will use this diagnosis to represent uncomplicated continued opioid use, which is therefore much different that an opioid use disorder or overdose. "Chronic, uncomplicated opioid use" has an ICD9 code of 304.00, which is the same as "opioid dependence." These overlap with opioid use disorder ICD9 codes, and it is an inherent challenge of administrative data. The other diagnoses included are clearly misuse/abuse; however, the majority of the cohort (n=2203) have this more nebulous diagnostic code. It would not be surprising that those patients that continue to get refills are more likely to get this diagnosis, even if they are not misusing or abusing the opioid. In addition, I sometimes found the narrative unclear regarding misuse. For this to be considered a study of "misuse" the authors need to make a solid argument that these patients in fact are misusing or abusing.
2. Overdose- important to note that the ICD9 code for overdose may not be very sensitive, as this will not detect those who die, nor will it detect those who are resuscitate in the field (EMS) and do not seek care to follow. There are groups working to create these types of data, but it is not easy. This is a limitation you cannot overcome.
3. Analysis- for the association between opioid use and the rate of misuse, does the relationship hold true if you simply analyze the initial prescription? Given the outcomes definitions, it seems obvious that refills would increase the rate of "opioid dependence," if that includes chronic uncomplicated opioid use. Confused, as Fig2A calls it "initial exposure" but the prose states that you analyzed duration of exposure by week including refills.
4. Days supplied vs dose- I am surprised that you do not see a more clear association with dose. While days supplied is a measure in claims data, it is not really how clinicians think when they prescribe. There may be some sense of an approximate time, but in the end, physicians prescribe a number of pills with less thought on the days this is intended to cover. We also found a weak association with dose when considering new chronic use of opioids.

Additional comments:

1. Abstract- Concept of "duration" of opioid prescription is confusing, as many will assume this means the first prescription; however, this is about refills
2. Abstract- should clearly describe that this is a composite measure for the primary outcome
3. P5- why not match the medical and pharmacy coverage? Seems that you would want a longer assessment of opioid use before and after surgery to match your medical outcomes.
4. P5 bottom- members were followed until they experienced an outcome or last month of coverage---why vary the coverage?
5. Methods- would be good to include a supplement of the CPT codes included to derive the cohort, as well as those used as covariates.
6. P6- 30-day postop for inclusion for postop opioid use is liberal. I would suggest a 3-7 day window to ensure that you can relate the script to surgical care—see Barnett NEJM 2017 Emergency Medicine
7. Did you do a subanalysis of those using opioids for <7days before surgery—these people may not really be "naïve"---at minimum, my sense is that they may behave differently
8. P7 given the primary outcomes, why truncate the refills to 5? Did you only exclude those with >350mg OME in the first prescription
9. P7- why require that there not be a 30 day gap in prescribing? Getting a refill after a month could still be relevant to your outcoems---you are not trying to define chronicity but instead the effect of prescribing on dependence, abuse, overdose---so, all scripts seem relevant to me
10. Results- our group recently published an article that found no association between the initial prescription size and refill rate---seems relevant to this work and should be considered.
11. Table 1- why not consider age at time of surgery instead of birth year?

12. Figure 1- I would again prefer age at the time of surgery if you decide to keep Figure 2B in this manuscript. I wonder, however, if it is worth it to include Figure2B. There are some distinct findings, but the concept is the same.
13. P12, line25-27- I do not follow this comment. All were opioid naïve preop.
14. Figure 3a- why MME/day instead of MME? Total MME accounts for dose and duration and may be a better measure.
15. P14- second sentence of discussion- again, you describe "abuse" and "overdose" but some of this may have been what a physician deemed to be uncomplicated chronic use or dependence.
16. Discussion- I like that you refer back to the figures in the discussion

Additional Questions:
Please enter your name: Chad M. Brummett, MD

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Institution: University of Michigan

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A fee for organising education?: No

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