Author’s response to reviews

Title: Postoperative Opioid Requirements of Patients Receiving Sublingual Buprenorphine-Naloxone: A Case Series

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Postoperative Opioid Requirements of Patients Receiving Sublingual Buprenorphine-Naloxone: A Case Series
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BMC Anesthesiology

To: Mr. Guangde Tu
Editor
BMC Anesthesiology
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Dear Editor-in Chief,

Thanks you for giving us opportunity to respond to reviewers’ comments. We addressed all their questions/suggestions, and we believe that their remarks substantially improved our manuscript. Included is a cover letter with point-by-point responses to the comments. Please note that we highlighted all changes made in the revised manuscripts. Finally, we deleted Figure 2, as is related to using the data from historical controls from the European group which reviewer #1 deemed not needed. We also changed the title to read ‘Perioperative’ rather than ‘Postoperative’ as we account for all opioid use including that from the start of surgery.
We look forward to receiving your decision regarding our manuscript.

Sincerely,

Yvette Martin McGrew, M.D., Ph.D
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Responses to Reviewer 1:

This report is a case series of 24-hour postoperative opioid requirements and peak pain intensity scores in patients presenting for diverse operations and who had received buprenorphine-naloxone (Suboxone) within 30 days before undergoing surgery. It appears to be a convenience sample drawn from data captured in one quaternary medical center from 2005-2016; it is not clear to this reviewer whether the authors view their case finding method as capturing all relevant cases.

Response: Cases were identified by an electronic search of our medical records with proprietary software. Using the search criteria we identified all patients who were known to have received any form of buprenorphine (buprenorphine, buprenorphine/naloxone, Suboxone) within 30 days antecedent to a surgical procedure. All charts were reviewed to ensure inclusion criteria for this study. Using this methodology, we included all patients using Suboxone and undergoing surgery with anesthesia during the given time period. While we agree this is a convenience sample, our methodology was applied consistently across the study period, and we believe captured all relevant patients. This methodology is now further described in the Methods section.

At a time when many clinicians are facing an increasing need for data upon which to base management decisions for increasing numbers of patients presenting for surgery while taking Suboxone, the data presented are of great current interest. The manuscript is clear and well-written.

Response: Thanks

On the other hand, the use of essentially historical controls from a European sample may be questioned, given that there may be differences in premedication, dose of Suboxone employed, relative proportions of different types of operation, patient expectations and education, or intraoperative surgical and anesthetic technique between North America and Europe.

Response: The use of the European reference group was to obtain expected pain intensity after specific surgeries in patients not receiving Buprenorphine. However, we agree that there may be difference in expectations or intraoperative surgical and anesthetic technique between North America and Europe. In addition, patients in the present study include a mix of Suboxone treatment strategies (interrupted vs uninterrupted, variable doses, variable timing of preoperative discontinuation). For this reason we have deleted the comparison to the European practice reference from the revised manuscript including Figure 2 which graphically depicted opioid use in regard to expected scores.
It would seem more internally valid to compare opioid requirements for patients treated at the same institution, but differing with respect to recent Suboxone exposure. The European data could be mentioned briefly in the Discussion but the statistical comparisons would be based upon patients observed only in the authors' institution, matched according to the type of surgical procedure.

Response: In the present series, patients were on variable Suboxone treatments, some interrupted some not, and those who were interrupted were interrupted at variable times before surgery. For this reason, we do not feel that creating a group of ‘procedure matched controls’ would provide any additional information what we offer in the present manuscript. Therefore, we would like to present our current data exclusively as a case series (as we stressed in the title), where providers can look at specific case, and get a sense for case-specific clinical scenario opioid use.

Nonetheless, we recently published a case control study on opioid requirements for patients on uninterrupted buprenorphine (transdermal form) treatment undergoing surgery. In this study we included a control group and abstracted all relevant postoperative opioid requirements and pain scores. This paper is published in RAPM, and now is cited in our Reference list as: Martin YN, Pearson ACS, Tranchida JR, et al. Implications of Uninterrupted Preoperative Transdermal Buprenorphine Use on Postoperative Pain Management. Reg Anesth Pain Med 2019;:1–6. doi: rapm-2018-100018 In our revised manuscript (discussion) we now describe the opioid requirements for the buprenorphine patients and controls from that study. Although no formal conclusion can be made, based on the level of opioid requirements in patients in the present study relative to our prior study we believe it is appropriate to state that the ‘amount of opioids administered for patients in the present case series likely exceeds that expected for patients undergoing similar procedures and not receiving long-term opioids.’

It was helpful for this reviewer to see in the case report presented within the box, and in the footnote to Table 2, the components of the multimodal management approach provided for that patient (e.g., coadministration of ketamine). The authors themselves suggest (bottom of page 10 to top of page 11) that multimodal therapy may benefit this patient cohort.

Response: Thanks

If feasible, could the different types of operation be presented along with typical components of the perioperative multimodal regimen including relevant anesthetic management? Providing such information would help place the findings in context, e.g., if nonopioid adjuvants were little used for one type of operation during the earlier years of observation, and unimodal pain relief with opioids was the standard of care, then one might expect to see greater postoperative opioid consumption after Suboxone exposure in patients observed during the earlier years.

Response: The types of surgery are provided in the Tables. All preoperative adjuvant pain management treatments were shown in the Table 2 footnote. It is also indicated under “type of surgery” whether procedure was open vs laparoscopic and year when procedure was done. In the revised manuscript we indicated in Tables 1 and 2 all anesthetics used (main agents for general anesthesia and local anesthetics and other pertinent drugs used during for regional anesthesia) ketamine and ketorolac given if first 24 postoperative hours (symbols with corresponding footnotes). Year of surgery is given to provide readers with opportunity to analyze assessment of management patterns, s which we do not notice. Since proper preplanned multimodal pain management was implemented in only one patient (Box. Post Hoc Case Report) we cannot comment on the role of multimodal pain management on opioid requirements in these patients, specifically since we do not a consistent pattern of non-opioid
management. This is reiterated in our Discussion.

Similarly, if one had a sense of whether the same operation was more likely to be performed using a minimally invasive technique in later years, this might be of interest.

Response: All types of procedures and surgical approach are listed in the Table. There were few laparoscopic procedures (see Table) and the nature of procedures (orthopedic etc.) is such that not substantial conversion to minimally invasive approach occurred over the time frame of this study.

Finally, the authors present data as to whether a pain consultation was requested but one wonders what the threshold was for obtaining such a consult, whether the requests were filed preoperatively and expectantly, or only after postoperative pain proved difficult to control.

Response: It is very difficult in retrospective manner to answer this question. However, in principle, in our practice preemptive ‘pain service management’ applies to patients with continuous regional anesthesia catheters (anesthesia pain management team manages infusion rates and adjuvant analgesic therapies). For those with single shot regional block, and in those with general anesthesia only, the surgical service is primarily responsible for prescribing postoperative pain medications, and the anesthesia pain service is consulted only in cases of inability to controlled pain by primary service. We added this information to the manuscript.

This reviewer recognizes the extra work required to address these suggestions, and accepts it may not be feasible to do so, but offers them so as to increase the impact of this case series at a time when clinicians are still looking to expand the published clinical experience such as presented herein.

Response: Thanks for the understanding.

On page 5, line 56, shouldn't the NRS be 0-10 not 1-10? Another minor question is whether the more current term "PACU" should be used in place of "RR".

Response: These changes have been made.

Responses to Reviewer 2:

Thank you for your time and effort in conducting this study and preparing this manuscript. This has been a controversial topic for some time. There are little to no high-quality clinical research data to make decisions. The original protocol we wrote at Michigan were initiated based on a few cases that were incredibly challenging to manage, including one we published in the Journal of Opioid Management---any of these cases would be enough to change the results of a case-control or retrospective study—there are many more such case reports in the literature and we have many that were not published, as we were concerned about the bias of case reports. With that said, times have changed from when we first wrote the protocol, and many have misinterpreted the protocol to include patients with opioid use disorder---we do not recommend weaning for those with OUD, unless suggested by their addiction provider.

I believe that the manuscript adds to the literature; however, there are some changes needed.

Response: Thanks for the comment.
Overall comments/major critiques:

1. Conclusions- it is really not possible to make a strong conclusion in either direction regarding what to do with buprenorphine before surgery. This a very small, heterogeneous cohort, hence between group comparisons suffer from overwhelming bias. Just reading through the description supports this concern—many different types of surgery and anesthetic management and small n/group—this is why we have not done these analyses in past. Even within the cessation group, there is likely a meaningful difference between those who stop for 1 day and those who stop for more. Moreover, some would likely have been switched to other opioids in lieu of buprenorphine, while some may have been weaned off without replacement. I believe the conclusion to your introduction and the manuscript must note that the cohort was heterogeneous and small, hence, recommendations cannot be made based on these data alone. Note, I certainly respect that many do not agree with our current protocol, and we anticipate a modification that would include a shorter cessation period.

Response: Excellent comment, we entirely agree with this reviewer, we added this sentence to our conclusion.

2. Buprenorphine continuation- were they continuing it during their post-op care? If so, this should be included in the morphine equivalency.

Response: None of these patients had Suboxone continued during the first 24 postoperative hours, and this is indicated in the results section.

3. Outcome of interest- you state that the goal was to understand whether regional reduces opioid requirements---this would be expected given the available data—this cohort is underpowered to detect a difference.

Response: You are absolutely right, and we added this to discussion. However, one would expect that with efficient continuous regional anesthesia opioid requirements would be drastically reduced. However, regional treatment was not protocolized for patients treated with Suboxone in present study, but rather management followed the usual clinical practice, and therefore reduction of opioid usage was not noticed.

4. Determination of buprenorphine cessation- how did you determine this---not likely a set variable, and my sense is that it is not reliably assessed on all patients. Should be better defined in the methods.

Response: On admission to Mayo Clinic all medications are reviewed with the patient by a registered nurse, and it is noted the time of last medication taken. We included only patients where we were able to identify the time of the last Suboxone dose taken. Any patient that did not have this information was excluded. This information is included in the Methods section.

5. Should not call it "Suboxone" throughout---I would just make a statement that you will refer to it as buprenorphine throughout—it is the same med whether including naloxone or not, unless it is injected, which is not relevant here.

Response: Agree, and we have changed it to SL-BUP (sublingual buprenorphine). Sometimes we refer to other forms of buprenorphine, that are administered transcutaneously, so replacing
Suboxone with buprenorphine throughout the text would be misleading, as different routes of buprenorphine may have different effects.

6. Minor- do not abbreviate "RR"- can spell it out throughout

Response: Pre request of another reviewer, we now use PACU.

Specific comments:
1. Comment about naloxone in the abstract intro can be deleted. Conceptually true but it is really not that big of a factor. You note this appropriately in the intro of the manuscript, but not important enough for abstract.

Response: Thanks for the comment. We did it as suggested.

2. P 9, line 43- "(Box)"? patient name?

Response: We refer to Box in revised manuscript: as (see Box. Post Hoc Case Report). E cannot provide patient came due to strict patient confidentiality policy we have to follow.

3. P10- just include your in press article in the references.

Response: Done and provided as reference 16 in the revised manuscript.