PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quantity of opioids consumed following an emergency department visit for acute pain: a Canadian prospective cohort study.
AUTHORS	Daoust, Raoul; Paquet, Jean; Cournoyer, Alexis; Piette, Éric; Morris, Judy; Gosselin, Sophie; Émond, Marcel; Lavigne, Gilles; Lee, Jacques; Chauny, Jean-Marc

VERSION 1 – REVIEW

REVIEWER	Patricia Newcomb, PhD, RN Texas Health Resources, U.S.A.
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	Review comments Enjoyed reviewing the paper about opioid prescribing patterns in EDs. I believe the authors made their point well. Logical flow is good. Data supports conclusions. The comments below suggest a few minor edits that might help the paper. Best wishes. 1. Very nice use of English, but still needs to be proofed to correct the few grammatical errors and awkward sentences that exist. I assume the BMJ copy editor will provide this service. 2. Statements about strengths and limitations do not indicate which activities are strengths and which are limitations from the authors' perspective. Given that the proportion of returned diaries was "low," it is probably misleading to state that the follow-up phone calls 'validated' the diaries. Instead, consider that items 2 and 3 reflect the same limitation, i.e. the use of self-reported data, and could be combined without mentioning validation. (see comment #6) 3. Page 5, line 17 mentions "Americans." Since this sentence immediately follows a sentence that speaks about the U.S. and Canada, you might consider clarifying that the 10 million "Americans" in line 17 are residents of the U.S. Although the paper is written by Canadians, the data that the authors use in the text to justify claims about narcotic misuse is all from the U.S. Would you consider including some Canadian data in the text, as well? [There are some Canadian references in the reference list, but no mention of Canadian findings in text]. 4. Page 7, line 50. Does "adequately supply" mean adequately manage pain in 80% of patients with a complaint of acute pain? Consider clarification so reader is not forced to read Hill. 5. In the discussion of the power analysis, is it really important to divulge how long the authors thought it would take to accrue the sample? Consider removing this phrase since the study period is reported in a following section. 6. Page 8, line 40. The authors are discussing validation of the diaries (see comment #2) using intraclass correlation. That is great, but the reader is never told how many diaries were actually returned. Earlier in the paper, it was suggested that only a small fraction of

	diaries were returned. If only a small percentage were returned it might be a stretch to conclude that the diaries are consistent with interviews in spite of statistical testing. The text seems to imply that ALL patients, or most, were interviewed by phone. If only patients who did not return diaries were interviewed, this needs to be clear in the text. It was also not clear in the methods section how the diaries were returned – were they mailed (via postal service) back to the ED? 7. Page 10, line 13. The sentence about unused narcotics is not perfectly clear (to me). Does “renal colic (81%)” mean 81% of the renal colic patients did not use all their opioids? Or does it mean renal colic patients as a group did not use 81% of their opioids? 8. Consider including more details in the methods section regarding diaries and interviews in case other investigators would like to replicate the study. For instance, who performed interviews? How were diaries retrieved?

REVIEWER	Jay S. Lee, MD University of Michigan Ann Arbor, Michigan United States of America
REVIEW RETURNED	04-May-2018

GENERAL COMMENTS	This is a single-institution, prospective cohort study evaluating opioid prescribing and patient-reported opioid consumption in a sample of patients discharged from the emergency room with an opioid prescription for acute pain. They found that patients consume significantly less opioid than prescribed. The research question is clearly defined and highly relevant given the current opioid epidemic. The study is well-designed to answer this questions, and the findings have the potential to change opioid prescribing practice ED physicians. The paper is generally well-written. The two key limitations of this study are: 1) unknown amount of selection bias due to the convenience sample; and 2) single institution study limits generalizability. These should be addressed before considering the manuscript for publication. Specifically, the authors state they were not able to determine the number of patients missed by the ED physicians. I am interpreting this to mean that authors do not know the total number of patients who were seen in the ED for acute pain during the study period. There may be considerable selection bias because of this, and readers must have some information about this. For example, the authors report that 1315 patients were initially contacted for the study. How many patients were not contacted for inclusion in the study? If there were only 100 patients who were not contacted, this would reflect a small degree of selection bias and would strengthen the study. I suspect, however, that many more patients were seen for acute pain in the ED during the study period. The patients contacted for inclusion in the study could be substantially different from those who were not contacted. This limitation is also not adequately addressed in the discussion section, and the authors should provide more explanation about how it could impact the findings. The authors do an outstanding job evaluating the patients who were contacted, but not included in the study in Table 1. They must make at least some attempt to quantify how many patients were not even contacted for the study. The second major limitation is that it is a single-institution study. The findings are still valuable, but this limits the generalizability of the results. I fundamentally disagree with the authors’ assertion that it

	"would be surprising if patients consume opioids differently in other settings" (discussion section). This assertion is not supported by data from other studies. In fact, there may be substantial variation between hospitals for the amount of opioid prescribed or the amount of opioid consumed by patients. For example, in a teaching hospital with trainees who constantly rotate, the trainees may not be adept at counseling patients on appropriate opioid use (i.e. use non-opioid analgesics first with opioids only for breakthrough pain) or the risks of opioids. Patients at a different non-teaching hospital with more experienced practitioners may consume less opioid because they were counseled more effectively on appropriate opioid use. Alternatively, what if the patients seen at this hospital are substantially different from other hospitals? They could have higher rates of mental health disorders (anxiety and depression) or fibromyalgia phenotypes, which have been associated with increased opioid consumption for acute pain in surgical patients (Janda et al 2015 Pain Medicine). This limitation must be addressed in more detail in the discussion section. I also have several minor points in the manuscript that should be improved. For the abstract, please describe the 5 categories for acute pain conditions used in the study. I also suggest removing all instances of the abbreviation "M5E" in the abstract and manuscript. This is jargon which will confuse readers. Instead, write out "X tablets of 5 mg morphine," which is easier to interpret. Also, do not list the number of pills needed to meet needs of 80% of all patients. You have more granular data than this. List it by procedure, or not at all. Readers may misinterpret this as suggesting they can prescribe 20 pills to all acute pain patients in the ER, which is not true. In fact, your study findings demonstrate some pain conditions require less than 20 pills (i.e. renal colic and abdominal pain), while others may require more (fractures). Also, when reporting medians, please replace "Q1-Q3" with the interquartile range (difference between Q3 and Q1). For the results section, please use subsection headings to divide the results section according to your key findings (i.e. description of study cohort, opioid consumption, percentage of unused opioids). This will make the results section easier to skim for readers. For the methods section, the authors report a low response rate for the 14-day diary as a justification for conducting a telephone survey. This is reasonable; however, the authors should provide data on the response rate for the diary, and what % of the collected data was from phone survey vs. returned diaries. Also in the methods section, the description of the pain conditions should be placed in its own subsection (it is not an outcome). For the description of the analysis, please explicitly state the null hypothesis in the first paragraph. A parenthetical description "(<10)" is not sufficient. Your power calculation also appears to based on a one-sided P-value, and this should also be explicitly stated. In addition, when describing the analysis for comparing the quantity of opioid across pain conditions, the description of "two-by-two comparisons" is too vague and needs more specific details about which groups were compared.

REVIEWER	Mieke van Driel University of Queensland, Australia
REVIEW RETURNED	16-May-2018

GENERAL COMMENTS	This is a clear and well conducted study that provides insight into a potential driver of opioid misuse. It raises a number of issues related

	to common practice that can be addressed to minimise potential harmful use. The findings underpin an important message to prescribers, i.e. to think beyond their prescription on the day of encounter and dsicharge! There are a few points that could be clarified further and a few other suggestions to incorporate in the discussion. Points for clarification: - page 6, selection of patients: what is your sampling frame? data is provided on people who were approached but not included, but doesn't include those missed. The total sampling frame could be retrieved from medical records? - page 6: patients were recruited by research nurses, 24/7??? - page 7, line 34: this suggests that only people who did not return their diary were phoned, whereas from the text later on it seems all were phoned? The flowchart indicates only a proportion were phoned. Please clarify. - page 8, line 30: does this refer to pill count or M5E? - page 9, line 14: can you specify the reasons for exclusion? - what do you know about those lost to follow up? Discussion: Although the discussion is well structured and within the scope of the findings it is a bit 'light' on what can be done to move forward, what can this study contribute to better quality use of medicines and reducing harm to patients? - every clinician will know that renal colic for instance doesn't need to be treated with 2 weeks of opioids, so why is this happening? could this be related to packet size of dispensed opioids or is this a local guideline or protocol? - the authors mention the variability in analgesic needs between different conditions, yet the conclusion suggests another 'one size fits all' approach albeit it at a lower pill count? - I acknowledge that this paper focuses specifically on opioid prescriptions but pain management is much more subtle than that. For instance, not all patients were prescribed paracetamol and/or nsaids which would be the first step? Another logical way to reduce opioid prescribing is to focus on non-opioid analgesics before launching into opioids. Therefore, I think this issue needs a place in the discussion of your findings. - this study is situated in an ED but after patients are discharged they go back to the community and care of their GP. Have you considered the role of GPs in en- or discouraging use of opioids? - what do you suggest to change in the practice at your ED and how is this transferrable to other EDs? The last sentence: "ED physicians should adapt their prescription practice to minimize unused opioids." is a very generic motherhood statement. Knowing how difficult it is to change doctors' habits, what have you learned form this study that can facilitate this change?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

Reviewer Name: Patricia Newcomb, PhD, RN Institution and Country: Texas Health Resources, U.S.A.
Please state any competing interests or state ‘None declared’: None declared

Enjoyed reviewing the paper about opioid prescribing patterns in EDs. I believe the authors made their point well. Logical flow is good. Data supports conclusions. The comments below suggest a few minor edits that might help the paper. Best wishes.

1. Very nice use of English, but still needs to be proofed to correct the few grammatical errors and awkward sentences that exist. I assume the BMJ copy editor will provide this service.
Response: The paper was originally revised for English but we are open to every BMJ editor suggestions.

2. Statements about strengths and limitations do not indicate which activities are strengths and which are limitations from the authors' perspective. Given that the proportion of returned diaries was "low," it is probably misleading to state that the follow-up phone calls 'validated' the diaries. Instead, consider that items 2 and 3 reflect the same limitation, i.e. the use of self-reported data, and could be combined without mentioning validation. (see comment #6)
Response: Done. We changed items 2 and 3 according to the reviewer comment:
- "First large study to prospectively document opioids consumption after an acute pain emergency department visit."
-"Opioid consumption data from diary or phone interview could be biased by self-report."

3. Page 5, line 17 mentions "Americans." Since this sentence immediately follows a sentence that speaks about the U.S. and Canada, you might consider clarifying that the 10 million "Americans" in line 17 are residents of the U.S. Although the paper is written by Canadians, the data that the authors use in the text to justify claims about narcotic misuse is all from the U.S. Would you consider including some Canadian data in the text, as well? [There are some Canadian references in the reference list, but no mention of Canadian findings in text].
Response: Done. We changed the sentence to add Canadian opioid misuse prevalence: "Over 10 million US citizens have misused opioids at some point in their life and 82,000 Canadians (0.3% of the total population) had non-medical use of prescription opioids in 2015."

4. Page 7, line 50. Does "adequately supply" mean adequately manage pain in 80% of patients with a complaint of acute pain? Consider clarification so reader is not forced to read Hill.
Response: Done. We clarified this statement: **"**that would adequately supply for two weeks 80% of patients."

5. In the discussion of the power analysis, is it really important to divulge how long the authors thought it would take to accrue the sample? Consider removing this phrase since the study period is reported in a following section.
Response: Done. We removed that part of the sentence. "To detect a significant difference from the null hypothesis (<10) using a Wilcoxon test assuming non-parametric distribution, we had to recruit at least 499 patients to achieve a power of at least 0.80 with an alpha of 0.05 (PASS version 11.0; NCSS, LLC. Kaysville, Utah)."

6. Page 8, line 40. The authors are discussing validation of the diaries (see comment #2) using intraclass correlation. That is great, but the reader is never told how many diaries were actually returned. Earlier in the paper, it was suggested that only a small fraction of diaries were returned. If only a small percentage were returned it might be a stretch to conclude that the diaries are consistent with interviews in spite of statistical testing. The text seems to imply that ALL patients, or most, were interviewed by phone. If only patients who did not return diaries were interviewed, this needs to be clear in the text. It was also not clear in the methods section how the diaries were returned – were they mailed (via postal service) back to the ED?
Response: Done. We added in the results section (information that was present in the flow chart only) the number and % of patients who returned the diary, those who answered the phone interview and those who completed both assessments: "Among the 627 participants, 385 (61%) of them returned the 14-day diary, 547 (87%) patients responded to the phone interview, and 310 (49%) had completed both assessments."
We also add in the measurements section a sentence about how the diaries were returned: "Using pre-addressed and pre-stamped envelopes, these diaries were mailed back by the patients after completion." and that all patients were interviewed by phone: "all patients were also interviewed over

the phone by a research assistant and responded to five brief questions concerning their pain medication use and current pain intensity."

7. Page 10, line 13. The sentence about unused narcotics is not perfectly clear (to me). Does "renal colic (81%)" mean 81% of the renal colic patients did not use all their opioids? Or does it mean renal colic patients as a group did not use 81% of their opioids?
Response: Done. We changed the sentence to be clearer that it is 81% of their opioids that were not used: "The percentage of unused opioids showed significant differences across pain conditions ($p<0.01$): patients suffering from renal colic and abdominal pain conditions did not use 81% and 78% of their opioids, respectively, and these were significantly higher than patients suffering from musculoskeletal, fracture, or "other" pain condition (62% when averaging the 3 categories; Figure 2).

8. Consider including more details in the methods section regarding diaries and interviews in case other investigators would like to replicate the study. For instance, who performed interviews? How were diaries retrieved?
Response: See response to comment # 6.

Reviewer #2:

Reviewer Name: Jay S. Lee, MD
Institution and Country: University of Michigan, Ann Arbor, Michigan, United States of America Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below. This is a single-institution, prospective cohort study evaluating opioid prescribing and patient-reported opioid consumption in a sample of patients discharged from the emergency room with an opioid prescription for acute pain. They found that patients consume significantly less opioid than prescribed. The research question is clearly defined and highly relevant given the current opioid epidemic. The study is well-designed to answer this question, and the findings have the potential to change opioid prescribing practice ED physicians. The paper is generally well-written.

The two key limitations of this study are: 1) unknown amount of selection bias due to the convenience sample; and 2) single institution study limits generalizability. These should be addressed before considering the manuscript for publication. Specifically, the authors state they were not able to determine the number of patients missed by the ED physicians. I am interpreting this to mean that authors do not know the total number of patients who were seen in the ED for acute pain during the study period. There may be considerable selection bias because of this, and readers must have some information about this. For example, the authors report that 1315 patients were initially contacted for the study. How many patients were not contacted for inclusion in the study? If there were only 100 patients who were not contacted, this would reflect a small degree of selection bias and would strengthen the study. I suspect, however, that many more patients were seen for acute pain in the ED during the study period. The patients contacted for inclusion in the study could be substantially different from those who were not contacted. This limitation is also not adequately addressed in the discussion section, and the authors should provide more explanation about how it could impact the findings. The authors do an outstanding job evaluating the patients who were contacted, but not included in the study in Table 1. They must make at least some attempt to quantify how many patients were not even contacted for the study.
Response: Done. We agree with the reviewer that many more patients than those included in our study were seen for acute pain in our ED during the study period. However, a very small portion of them received an opioid prescription at ED discharged which is one of our inclusion criteria. Considering that our research nurses were regularly monitoring and informing ED physicians about the research protocol, we think that the number of eligible patients that we missed was not very high. Nevertheless, we agree with the reviewer that we did not address this point sufficiently in the limitation. We changed the limitations section accordingly: "The convenience sample (investigators could not reliably determine the number of missed patients) from one ED centre and the small sample size for less frequent pain conditions (especially abdominal pain) limit the generalization of our results." and added "There results should be confirmed in a multi-centre prospective study"

The second major limitation is that it is a single-institution study. The findings are still valuable, but this limits the generalizability of the results. I fundamentally disagree with the authors' assertion that it "would be surprising if patients consume opioids differently in other settings" (discussion section). This assertion is not supported by data from other studies. In fact, there may be substantial variation between hospitals for the amount of opioid prescribed or the amount of opioid consumed by patients. For example, in a teaching hospital with trainees who constantly rotate, the trainees may not be adept at counseling patients on appropriate opioid use (i.e. use non-opioid analgesics first with opioids only for breakthrough pain) or the risks of opioids. Patients at a different non-teaching hospital with more experienced practitioners may consume less opioid because they were counseled more effectively on appropriate opioid use. Alternatively, what if the patients seen at this hospital are substantially different from other hospitals? They could have higher rates of mental health disorders (anxiety and depression) or fibromyalgia phenotypes, which have been associated with increased opioid consumption for acute pain in surgical patients (Janda et al 2015 Pain Medicine). This limitation must be addressed in more detail in the discussion section.
Response: Done. We agree with the reviewer. We changed the limitations section according to the reviewer comment: "It is also possible that hospitals with different populations or different opioid approach treatment (non-opioid analgesic first and opioids for more intense pain) could change opioid consumption."

I also have several minor points in the manuscript that should be improved. For the abstract, please describe the 5 categories for acute pain conditions used in the study.
Response: Done. We add that information in the abstract: "We examined the quantity of opioids consumed by emergency department (ED) discharged patients after treatment for an acute pain condition (musculoskeletal, fracture, renal colic, abdominal pain, and other) and the percentage of unused opioids available for potential misuse."

I also suggest removing all instances of the abbreviation "M5E" in the abstract and manuscript. This is jargon which will confuse readers. Instead, write out "X tablets of 5 mg morphine," which is easier to interpret.
Response: Done. We changed the abbreviation M5E to tablets of 5 mg morphine throughout the manuscript.

Also, do not list the number of pills needed to meet needs of 80% of all patients. You have more granular data than this. List it by procedure, or not at all. Readers may misinterpret this as suggesting they can prescribe 20 pills to all acute pain patients in the ER, which is not true. In fact, your study findings demonstrate some pain conditions require less than 20 pills (i.e. renal colic and abdominal pain), while others may require more (fractures).
Response: Done. We replaced the result of all patients for each pain conditions in the abstract and results section: "The quantity of opioids to adequately supply 80% of patients was 20 tablets of 5 mg morphine for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other pain conditions. The quantity to adequately supply 95% of patients for three days was 15 morphine 5 mg tablets (or equivalent)."

Also, when reporting medians, please replace "Q1-Q3" with the interquartile range (difference between Q3 and Q1).
Response: Done. We changed Q1-Q3 to IQR throughout the manuscript.

For the results section, please use subsection headings to divide the results section according to your key findings (i.e. description of study cohort, opioid consumption, percentage of unused opioids). This will make the results section easier to skim for readers.
Response: Done. We added subsection headings in the results section.

For the methods section, the authors report a low response rate for the 14-day diary as a justification for conducting a telephone survey. This is reasonable; however, the authors should provide data on the response rate for the diary, and what % of the collected data was from phone survey vs. returned diaries.
Response: Done. We added in the results section (information that was present in the flow chart only) the number and % of patients who returned the diary, those who answered the phone interview and those who completed both assessments: "Among the 627 participants, 385 (61%) of them

returned the 14-day diary, 547 (87%) patients responded to the phone interview, and 310 (49%) had completed both assessments."

Also in the methods section, the description of the pain conditions should be placed in its own subsection (it is not an outcome).
Response: Done. We removed that part of the outcomes and located it under a new subheading: Stratification.

For the description of the analysis, please explicitly state the null hypothesis in the first paragraph. A parenthetical description "(<10)" is not sufficient. Your power calculation also appears to based on a one-sided P-value, and this should also be explicitly stated.
Response: Done. We changed the sample size formulation to be clearer: "To detect a significant difference from the null hypothesis (H_0=10) using a Wilcoxon test assuming non-parametric distribution, we had to recruit at least 499 patients to achieve a power of at least 0.80 with an alpha of 0.05, using a one-tailed test (PASS version 11.0; NCSS, LLC. Kaysville, Utah)."

In addition, when describing the analysis for comparing the quantity of opioid across pain conditions, the description of "two-by-two comparisons" is too vague and needs more specific details about which groups were compared.
Response: Done. We made all post-hoc 2X2 comparisons between painful conditions. We changed the formulation to be clearer; "All post-hoc two-by-two comparisons of the quantity of 5 mg morphine tablets consumed across pain conditions were made using Mann–Whitney U tests with Bonferroni correction for multiple testing."

Reviewer #3:

Reviewer Name: Mieke van Driel
Institution and Country: University of Queensland, Australia Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below This is a clear and well conducted study that provides insight into a potential driver of opioid misuse. It raises a number of issues related to common practice that can be addressed to minimise potential harmful use. The findings underpin an important message to prescribers, i.e. to think beyond their prescription on the day of encounter and discharge!
There are a few points that could be clarified further and a few other suggestions to incorporate in the discussion.

Points for clarification:
- page 6, selection of patients: what is your sampling frame? data is provided on people who were approached but not included, but doesn't include those missed. The total sampling frame could be retrieved from medical records?
Response: Done. Unfortunately no, medication prescription for discharged patients is not computerized in our institution and is not always available in the medical records. We agree with the reviewer that we did not address this point sufficiently in the limitation. We changed the limitations section accordingly: "The convenience sample (investigators could not reliably determine the number of missed patients) from one ED centre and the small sample size for less frequent pain conditions (especially abdominal pain) limit the generalization of our results." and added "There results should be confirmed in a multi-centre prospective study"

- page 6: patients were recruited by research nurses, 24/7???
Response: Done. We added that information in the selection of participants section: "Patients aged 18 years and older and treated in the ED from June 2016 to July 2017 were identified by ED physicians 24/7 and then recruited by research nurses."

- page 7, line 34: this suggests that only people who did not return their diary were phoned, whereas from the text later on it seems all were phoned? The flowchart indicates only a proportion was phoned. Please clarify.
Response: Done. We added information to indicate that all patients were phone interviewed also: "Partly because of the low percentage of the diary returned in our pilot study, two weeks post-ED visit, all patients responded were also interviewed over the phone by a research assistant and responded to five brief questions concerning their pain medication use and current pain intensity"

- page 8, line 30: does this refer to pill count or M5E?
Response: Done. This information is now added in the manuscript: "where we observed a consumption of 8.8 tablets of 5 mg morphine (SD=10) during a two-week follow-up."

- page 9, line 14: can you specify the reasons for exclusion?
Response: Done. We provided that information in the results section: "Of these, 29% had exclusion criteria (64% for language barrier, 33% for having chronic pain, and 3% for cancer pain),"

- what do you know about those lost to follow up?
Response: The characteristics of those who were lost to follow-up were similar to included patients as shown in table 1.

Discussion:
Although the discussion is well structured and within the scope of the findings it is a bit 'light' on what can be done to move forward, what can this study contribute to better quality use of medicines and reducing harm to patients?
Response: As mentioned in the manuscript, in light of our results, we can only suggest that ED practitioners adapt their opioid prescription to the painful conditions encountered at ED and to inform pharmacist to divide the prescriptions into portions. This would reduce considerably unused opioids that could be available for diversion.

- every clinician will know that renal colic for instance doesn't need to be treated with 2 weeks of opioids, so why is this happening? could this be related to packet size of dispensed opioids or is this a local guideline or protocol?
Response: It is not related to the packet size of dispensed opioids or local guideline since in Canada, there is neither such packet size nor general guidelines for opioid prescriptions. As mentioned in the manuscript, it is more: "This one-size-fits-all approach, which does not take into account the patient's individual condition, can probably be attributed to the lack of clinical data on opioid consumption." And also "The purpose of this over-prescribing may be to offset the inconvenience, for both patient and physician, of return visits to the ED or another medical service to obtain another prescription."

- the authors mention the variability in analgesic needs between different conditions, yet the conclusion suggests another 'one size fits all' approach albeit it at a lower pill count?
Response: Done. We changed the example to include both of our recommendations: "For example a physician could prescribe 15 tablets of 5 mg morphine for a renal colic (and be sure to supply the need of 80% of the patients) and ask the pharmacist to supply only 5 tablets at a time with an expiration date of the prescription in two weeks."

- I acknowledge that this paper focuses specifically on opioid prescriptions but pain management is much more subtle than that. For instance, not all patients were prescribed paracetamol and/or nsaids which would be the first step? Another logical way to reduce opioid prescribing is to focus on non-opioid analgesics before launching into opioids. Therefore, I think this issue needs a place in the discussion of your findings.
Response: Done. We added a sentence to discuss that important point: "Another way of reducing opioids consumption is for physicians to inform patients to try acetaminophen or NSAIDs first to reduce their pain before using opioids."

- this study is situated in an ED but after patients are discharged they go back to the community and care of their GP. Have you considered the role of GPs in en- or discouraging use of opioids?

Response: Recommendations of adapting opioid prescription to the painful conditions, to inform pharmacist to divide the prescription into portions, and to inform patients to try non-opioids before opioids to relieve their pain can also be applied by general practitioners.

- what do you suggest to change in the practice at your ED and how is this transferrable to other EDs? The last sentence: "ED physicians should adapt their prescription practice to minimize unused opioids." is a very generic motherhood statement. Knowing how difficult it is to change doctors' habits, what have you learned form this study that can facilitate this change?
Response: We added more information to facilitate change: “The quantity of opioids to adequately supply 80% of patients for two weeks was 20 morphine 5 mg tablets (or equivalent) for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other pain conditions. Also, 15 morphine 5 mg tablets (or equivalent) would adequately supply 95% of patients for three days. ED physicians should consider prescribing a smaller quantity of opioids and asking the pharmacist to dispense them in portions to minimize unused opioids.”

VERSION 2 – REVIEW

REVIEWER	Patricia Newcomb Texas Health Resources, USA
REVIEW RETURNED	11-Jul-2018

GENERAL COMMENTS	I thank the authors for their revision and am satisfied they have addressed the concerns stated in my initial review. In particular, limitations section much improved.

REVIEWER	Jay S. Lee, MD Department of Surgery, University of Michigan, USA
REVIEW RETURNED	28-Jun-2018

GENERAL COMMENTS	The manuscript is much improved and the authors should be commended for their excellent work. The authors have addressed all my concerns. I only have one additional suggestion outlined below: Introduction 4th paragraph: "Studies on ED opioid prescriptions draw their data from large retrospective administrative databases (25, 26), and therefore cannot distinguish between acute and chronic pain in their patients populations." Reference #25 is incorrectly cited here (study of surgical patients). I believe this should be reference #27 instead, which is an abstract from a conference (SAEM) that the authors later state is the pilot study for this paper. Please remove this or cite a different study published in a peer-reviewed journal. In addition, it is actually possible to identify opioid-naive vs. chronic opioid users from administrative data (Brummett 2017, JAMA Surgery). The author's correctly point out that the study from reference #26, does not make this distinction, but it is possible to do this. I recommend rephrasing as "...and did not distinguish between acute and chronic pain in their patients populations."

REVIEWER	Mieke van Driel University of Queensland, Australia
REVIEW RETURNED	28-Jun-2018

GENERAL COMMENTS	The authors have addressed the reviewers' concerns and comments well and I am happy with this revision.

VERSION 2 – AUTHOR RESPONSE

We remove the reference # 25 and change the sentence according to reviewer 2.

The changes are highlighted in yellow in the manuscript.