Peer Review File

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Reviewer A

Comment 1:

This is an important area where not much is known. The methods are rigorous and well defined. Results are clearly outlined. It would be good to know what percent toxicity occurred in patients with liver disease Vs. Others. However, I am not sure if you have this data available. Overall the findings and conclusions enhance the understanding of use of opioids and related meds among hospice patients with ESLD.

Reply 1: We do not have this data. We hope to encourage future studies to look into the potential toxicity and drug-adverse events occurred in patients with end-stage liver disease compared to other common hospice diagnoses.

Changes in the text: none

Reviewer B

Comment 2: Abstract –Conclusion – assumption made about adverse events of combining these medications and since the adverse events weren't studied in this specific study

Reply: We did not study the potential adverse events that may occur with combining opioids and CNS depressants. Therefore, we have simplified the conclusion to the overall result of the paper.

Changes in the text: Conclusion: We observed a high frequency of opioid and CNS depressant prescribing in a hospice patient population with ESLD which was similar to other common admitting hospice diagnoses. (page 2, line 36-37)

Comment 3: Key points –Given the OME were all the same across the diagnosis, I would not say 'significantly higher."

Reply: Removed "significantly higher" and indicated that the high dosage opioids prescribed were similar to other common hospice diagnoses.

Changes in the text: Hospice patients with liver disease were frequently prescribed opioids at high dosages (120 oral morphine equivalent), similar to other common hospice diagnoses such as cancer, cardiovascular, and respiratory disease. (page 3)

Comment 4: Implications – do all hospices have pharmacists to review? Or if available to have them review.
Reply: Yes, it is important to have clinical pharmacists in the interprofessional palliative care and hospice team. Understanding the pharmacology and implications of high prescribing in a vulnerable population such as end stage liver disease, clinical pharmacists have the skill set to provide this information for the team and contribute to safe and effective patient care.
Changes in the text: Added "clinical" pharmacists which are essential members of the team to individualize pharmacotherapy treatment plans to minimize symptom burden and medication-related adverse events. (page 3)

Comment 5: Intro –if using all terms such as ESLD, liver disease and cirrhosis please define these clearly or only use on term as this can be confusing to readers
Reply: Removed all references of cirrhosis and used only liver disease in reference to chronic liver disease, and added ESLD to patients with end-stage liver disease.
Changes in the text: Throughout page 2 to 10

Comment 6: Methods –Line 87 – missing cancer diagnosis in the list
Reply: Included cancer into list.
Changes in the text: Added "cancer" to the sentence: Hospice descedents who died while receiving hospice care were included in the analysis if they were 18 years of age and had a primary diagnosis of ESLD, cancer, cardiovascular, or respiratory disease (page 6, line 84-85).

Comment 7: Methods Line 108 – I think this study would be stronger with confidence intervals esp since the sample size is so high
Reply: Data analysis was improved by providing confidence intervals for groups that demonstrated any difference throughout the results section. Study methods have included confidence intervals to be included in the descriptive statistics used.

Changes in the text: Added “confidence intervals” (page 6, line 109). Added confidence interval differences throughout results section (page 7-8, line 128-155).

Comment 8: Limitation needs to be added all prns possible to calculate daily OME
Reply: Added to limitation section that all possible PRNs were included in total daily OME.
Changes in the text: Added to text “When calculating the assumed total daily OME, all possible PRN dosages were included which may not account for all actual doses patients were taking” (page 10, line 221-223).

Comment 9: Please define which medications were referenced as a CNS depressents was it just benzodiazapines and gabapentinoids, were anticholinergics or sedating antidepressents also included?
Reply: To clarify, we will add CNS depressants defined in the methods section.
Changes in the text: Added to methods section “CNS depressants included in this study were benzodiazepines, gabapentinoids, and opioids” (page 6, line 102-103).

Comment 10: Results Line 115 – how many patients had liver disease? I would add this here then give demographics for liver disease patients specifically.
Reply: Included this statistic for liver disease at the beginning of th results section as it fit better there. Added the prevalence of patients with ESLD.
Changes in the text: Added “This study included 119,424 hospice decedents in the analysis, with the most prevalent hospice diagnoses being cancer (46.2%) and about 2.2% of the patients with ESLD” (page 6, lines 115-116).

Comment 11: Results 125 – please include if these were statistically significant or not
Reply: Statistical testing was not completed for this data and percentages were compared to determine if they were similar or more frequently prescribed. Because the statistics and percentages were similar, the sentence was rephrased to state that prescribing was similar in patients with ESLD and cardiovascular and respiratory disease.
Changes in the text: Added “similar to” and removed “more frequently (page 8, line 125-126).

Comment 12: Lines 127-133: These numbers although numerically are different, seem clinically about the same, which I think highlights that symptom burden in the liver population matches those of cancer, resp and cardiac. Unless statistically significant I would limit saying these numbers are all that much higher.
Reply: Yes, I agree. Similar to comment 11, it is better to rephrase as similar to given the percentages were very close (<5%).
Changes in the text: Added "similar to" and removed "more frequently (page 7, line 140-144).

Comment 13: Discussion - I really like the idea of this paper and looking at hospice prescribing. Line 166- I disagree with this statement and without improved stats I'd be cautious of this statement that 120 is a lot more than 75 OME. Clinically one could argue these are not that different.
Reply: It is important to define "high dose opioids" therefore, we have included this detail in the paper and agree with comment that it can be stated that patients with ESLD had similar high dose opioids prescribed to other common hospice diagnoses.
Changes in the text: Added "typically defined as 90 or more OME" similar to other common hospice diagnoses (page 9, Line 183-184).

Comment 14: Line 168 - remove 'are high'
Reply: Removed "are high."
Changes in the text: Removed "are high" (page 9, line 185).

Comment 15: I agree that this being a large study is good, and is provided data about how much use compared to other illnesses, but to continually remind to cautious use without this being a study looking at adverse events is giving the wrong message. I think this study highlights the need of such medications and that symptoms of liver disease match if not are higher in freq than patients with cancer, renal disease, resp disease at the end of life.
Reply: The highlight of this study was to demonstrate the high prevalence of pain and symptoms as evidenced by opioid and CNS depressant prescribing which may not have as much focus as other common hospice diagnoses such as cancer, respiratory or cardiovascular disease. Therefore, future studies looking into the potential risks of drug-adverse events if clinicians are not thoughtful with dosing and medication selection is important for evidence-based medicine. However, we

agree that another highlight is to demonstrate the high burden of symptoms patients with ESLD experience that may not be as noticed as cancer or respiratory disease. Therefore, we agree to add this detail into the “Key Points” section.

Changes in the text: Added to Key Points – implications section, an additional bullet point detail of the high symptom burden patients with ESLD experience (page 3).