Peer Review File

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Reviewer Comments

Reviewer A

The authors have performed a comprehensive narrative review of pain management options in chronic kidney disease, highlighting the challenges with effective pain management in the renal population in different settings. The authors emphasise that there are discrepancies between what is recommended internationally for pain management versus what is available in low resource settings and have also provided tables of available opioids as well as guides to use. I would recommend more emphasis be placed on methadone's properties in Table 2 – methadone is not an easy drug to use with variable half-life depending on individual, and the potential to induce its own metabolism. It should be emphasized that methadone should only be used by experienced individuals as even though it has both neuropathic and nociceptive analgesic components, its pharmacokinetic properties make it potentially dangerous. It should always be titrated very slowly.

Reply: We have added the following additional information to emphasize the complex nature of methadone, along with a supporting reference. "The pharmacokinetics of methadone varies greatly from person to person and the potential for drug-drug interactions high. Due to its interaction with the voltage-gated potassium channels of the myocardium, methadone can prolong Q-T intervals. It's generally recommended to limit the use of methadone to experienced prescribers."

Emphasis on slow titration is in the table under dosing.

Reviewer B

This is a well-written review article that provides information on the epidemiology of pain and pharmacological approaches to treating pain in patients treated with CKM. It also provides a well-written over of CKM.

A novel aspect about this article as compared with prior articles on treatment of pain in kidney failure is its discussion of the challenges of pain management in low resource settings.

I have some general suggestions that may strengthen the article:

1. Greater discussion and a framework/strategy (ethical and practical) for approaching pain management in patients receiving CKM and in low resource settings when there isn't great evidence for practice but where the burden of pain is so great that doing nothing may also not acceptable. The authors touch on it with the need to use morphine in certain contexts where there really is no other pharmacological options.

Reply: We have paid careful attention throughout the manuscript to consider perspectives across diverse resource settings, including how the approach to pain

management may change in low resource settings and what therapies are unlikely to be available. We also expanded the discussion around morphine use when it is the only opioid available and the ethical imperative to address suffering (pgs 16-17).

2. Discussion of non-pharmacological approaches to treating pain, especially given its relevance to resource-poor settings where access to medications is difficult. I acknowledge that evidence for non-pharmacological approaches to treating pain is more limited than for pharmacological approaches. Still, there may be information learned from other patient populations that could be beneficial to patients with kidney failure.
Reply: Although we acknowledged the importance of non-pharmacologic management, it was initially beyond the scope of this article. However, given the relevance to pain management, especially where access to analgesics is limited, we have expanded the discussion and have provided what limited data there are on page 11, lines 204-220. Unfortunately, the evidence is limited and access to these approaches is also limited in LMICs.

3. Discussion of how to evaluate and track pain in a rigorous way so that providers and patients can assess whether treatment is working.
Reply: We have added a discussion on the importance of evaluating & tracking pain and available tools on pages 9 -10 under the new section titled "GENERAL APPROACH TO PAIN MANAGEMENT".

4. Discussion of how to formulate treatment goals with patient for pain management, given that complete relief of pain is often not possible.
Reply: We have added a discussion on the importance of recognizing the multifaceted nature of pain that extends beyond the physical realm, especially when caring for patients dealing with serious illnesses like KF. Given the multifaceted nature of pain, it's unlikely that all chronic pain can be fully mitigated through medication or conventional treatments. We have stressed the importance of negotiating realistic treatment goals that include the desired level of functionality and pain relief on pages 9-10 under the new section titled "GENERAL APPROACH TO PAIN MANAGEMENT".

I have some other minor suggestions for the authors to consider:

Title
1. Much of the content of the article is around delivering CKM (or more specifically, choice-restricted CKM) in the context of low- and middle-income countries and special considerations for this. Treatment of pain is also limited to pharmacological approaches. Perhaps the title should reflect this.
Reply: This is correct. The focus of this article was the pharmacological approach to pain management in CKM. However, after taking into consideration all the comments, the scope has been increased to expand on some general considerations around pain

management (including evaluation, tracking, negotiating treatment goals etc.) and non-pharmacologic approaches, especially given our attention to including the considerations relevant to low resource settings where access to analgesics is limited (as per your suggestions above). The main focus, however, remains pharmacologic considerations and this has been made clear in the abstract and introduction.

Abstract:
1. Benefits aside, CKM is also for patients who simply do not want to pursue kidney replacement therapy.
Reply: Yes, absolutely. We have made this explicit right upfront on page 4 at the end of the first paragraph of the introduction (line 68-69).

Manuscript:
1. Consider revising the subtitle "Adjuvants" to "Treatments for Neuropathic Pain."
Reply: We have changed this subtitle as suggested.
2. What about topical therapies, such as pramoxine, capsaicin and lidocaine for neuropathic pain?
Reply: While these have not been studied and applied to neuropathic pain in KF, there is some evidence for benefit in the general geriatric population, so we have added (pg 14, lines 269-273).
3. Although evidence is limited in general for pharmacological agents, I do think some acknowledgement of SNRI's for neuropathic pain is needed.
Reply: We have expanded slightly to state that "there is some evidence to support the use of selective serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors for neuropathic pain in the general population, data and clinical experience are insufficient in patients with KF to be able to make a recommendation." Pg 14, lines 275-278.
4. In the final paragraph, information on the limited training nephrologists in pain management might be better to share early on in the manuscript (perhaps under "Epidemiology of pain in CKM").
Reply: We have moved this section to the Introduction.

Reviewer C
This is an interesting article and raising important points regarding access to CKM in low income and low moderate income countries thanks for undertaking this publication
The main issues are grammatical and citations
see below for comments
Line 45 Grade 5 not category 5
Reply: The terminology in the manuscript is correct. "G5" stands for "GFR category 5".
Line 97 page 3 should be LIC not LMIC repeated twice
Reply: We have corrected this, thank you.
Line 122 – 126 pg 3 -4 needs a citation to support this statement

Reply: We think you are referring to “CKM… quite stable and live for several years while receiving CKM”. This has been referenced with two systematic reviews.
Line 128 – 130 page 4 also needs citation to support this
Reply: Line 132-134, page 7 “The increase of communicable diseases, particularly human immunodeficiency virus [HIV], malaria, tuberculosis, and an explosion of illicit drug use are also contributing to the increased incidence of KF.” This is now Ref (3, 24 and 25)
Line 133 – 141 – several statements and statistics provided with no citatations to support this
Line 142 – 152 – these statements also need to be supported by citation –
Reply: Line 142-152 “KF is associated with a high symptom burden globally that is experienced across age, sex, race, and geographic location, with chronic pain being one of the most prevalent and bothersome symptoms.” This is now in the INTRODUCTION (pg 5) and is now referenced with a recent systematic review and meta-analysis (ref. 12)
Line 164 – 166 pg 4 -5. Sentence is awkward and needs rewording
Reply: Line 164-166 is:“PHARMACOLOGIC APPROACH TO PAIN
General considerations…Pain is a complex biopsychosocial disease that can affect all aspects of life.” Perhaps you mean Line 171-173, now pg 12, line 225-228? We have reworded to “These patients and their families require specific psycho-social support, which includes the realization that this is a palliative pathway. Treatment may require forgiveness of previous drug abuse and containing ongoing addiction.”
Line 186 pg 5 – Many pains … awkward and needs rewording
Reply: We have reworded to simply “Pain….”
Line 196 – 201 - Detail re gabapentin clearance needs a citation to support this
Reply: Several references have been added to support the pharmacological statements for gabapentin (48), amitriptyline (49, 50) and acetaminophen (51).
And the same for the pharmacology properties of the medication identified - Amitriptyline , Acetaminophen ,
Additionally what would be ideal to further strengthen this publication would be the exploration of the non pharmacological management strategies (physical and behavioural therapies) and discussion regarding evidence to support this approach should be included. This will enable those who have limited access to pharmacological intervention to provide simple and sometimes effective care.
Reply: Thank you, we agree and have addressed this as per our response to Reviewer B, #2.

Reviewer D
The abstract needs to be restructured. It does not refer at all to the subject expected in the chosen title.
Reply: The abstract has been rewritten as per the Editor’s comments.
In my opinion, regardless of the content of the paragraphs "Conservative Kidney Management" and "Clinical Characteristics of People Receiving CKM", both should

be removed from the paper. The theme strongly deviates from the proposed focus "Pain in Kidney Failure".

Reply: We were asked to focus on CKM in this paper given the particular vulnerabilities and challenges with pain management in this population. The "Conservative Kidney Management" section was removed and integrated more succinctly into the INTRODUCTION as per the Editors' comment #4. The clinical characteristics of these individuals are also important given their extremely complex nature and high burden of complex comorbidity (see response to Editor's comment #4).

The paper should start with the paragraph "Epidemiology of Pain in CKM". I miss more references and, as a review article, it would be appropriate to explore "Pathophysiological" aspects already known recently involving crosstalk between pain and kidney injury.

In "Pharmacologic Approach to Pain", the paragraph that has more context within the expected theme is the "Approach to Analgesics", which should be restructured and expanded, including references and more aspects about multimodal therapy.

Reply: Thank you, we agree and have addressed this as per our response to Reviewer B, #2.

In "Approach to Analgesics", the real subtitle should be "Opioids", lacking to unify aspects of "opioids, active metabolites, renal clearing and avoided recommendations in CKM". In fact, what is exposed in table 3 does not fit well with table, forming the core of the subtitle "Opioids", and should be explored as a running text, with updated references.

Reply: We have reorganized starting with "NON-PHARMACOLOGICAL MANAGEMENT OF PAIN" as above followed by the "PHARMACOLOGICAL MANAGEMENT OF PAIN" section that starts with the more general principles before discussing specific classes of analgesics (see point below).

Finally, "Adjuvants" and "Non-Opioid Analgesics" should come next, after "Opioids", lacking to include new relevant aspects already published on non-pharmacological therapies or interventional approaches in this specific scenario, with references.

Reply: In the "PHARMACOLOGICAL MANAGEMENT OF PAIN" section we have reorganized the content so that it now unifies all the opioid related content (as suggested above), which comes after the neuropathic treatment (adjuvants) and non-opioids. Several new references have been added.

The text between lines 260-276 was fine, it is part of the context of the paper and can be explored in a better subtitle "Pharmacologic Approach to Pain in Kidney Failure". In this context, maybe even review the title - "Pain management in Adults with Kidney Failure?".

Reply: Agree. We have done this as outlined above.