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Letter: are opioid prescriptions associated with hepatic encephalopathy in patients with compensated cirrhosis?

Authors' reply

EDITORS,

We appreciate the letter from Li et al about our recently published article on the association between opioids and hepatic encephalopathy (HE).^{1,2} The letter raises interesting points deserving additional clarification.

While physicians worldwide may be cautious prescribing opioids, recent studies from the US demonstrate that opioids are prescribed at alarming rates for patients with cirrhosis.^{3,4} We found that opioid prescriptions are independently associated with incident HE in younger patients with well compensated cirrhosis,² validating similar findings from the US Medicare population.⁵ This adds to many other potential harms of opioids in cirrhosis, including hospital readmissions,⁶ overdose⁷ and decreased health-related quality of life.⁸ Furthermore, in a recent randomized trial of treatments for osteoarthritis and back pain, patients receiving opioids reported increased pain compared to the non-opioid group⁹ and, in cirrhosis, opioid use is associated with greater pain-related disability, even when adjusting for the severity of pain.¹⁰ Based on opioids' demonstrated risks, uncertain benefits and widespread use in the US, we feel justified in our conclusion that, when possible, opioids should be avoided in cirrhosis.

Without question, pain control is challenging in patients with cirrhosis given contraindications to commonly used analgesics like non-steroidal anti-inflammatory drugs. There are some situations when short-term opioids are indicated (e.g. post-operative pain). However, with a well-reasoned approach, we believe that opioid-sparing strategies are possible for most patients with cirrhosis. Clinicians should first identify and treat contributors to pain including comorbid sleep disturbances, anxiety/depression and substance use disorders.¹⁰ First-line pharmacologic options, including low-dose acetaminophen (<2 g/day) and topical analgesics, should be routinely offered. For

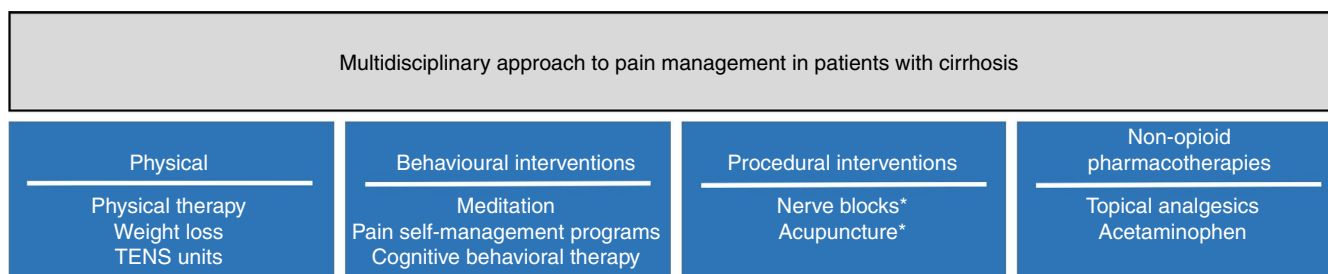
pain not responsive to first-line treatments, clinicians should pursue a multidisciplinary treatment approach including physical, behavioural, procedural and pharmacological aspects (Figure 1).¹¹ When patients do require opioids, clinicians should be vigilant to detect and prevent HE, including use of empiric lactulose and/or rifaximin.

Lastly, Li et al state that we did not account for the severity of liver disease or indications for opioid prescriptions. We used a national insurance claims database that does not contain laboratory data, thus precluding assessment of model for end-stage liver disease. However, we did account for liver disease severity by carefully controlling for decompensation events. We failed to find evidence that opioid prescriptions were associated with incident non-HE decompensation events, suggesting that our results were not confounded by the severity of the liver disease. In fact, the annual incidence of non-HE decompensation events was nearly identical in patients with no opioid prescriptions (12.0%), short-term opioids (12.0%) and chronic opioids (11.6%). Similarly, this database includes the type and duration of opioid prescriptions, but does not include information on the indication of opioids, precluding assessment of the 'appropriateness' of prescriptions. Nevertheless, this does not affect our conclusion that opioids, regardless of indication, were associated with an increased risk of HE.

In summary, given risks of opioids in patients with cirrhosis, we think their use should be limited. Broad employment of a multidisciplinary approach to pain in cirrhosis could reduce the high prevalence of opioid use and decrease the incidence of HE.

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TENS: transcutaneous electrical nerve stimulation; *caution in patients with coagulopathy

FIGURE 1 Multidisciplinary approach to pain management in patients with cirrhosis. TENS, transcutaneous electrical nerve stimulation. *Caution in patients with coagulopathy [Colour figure can be viewed at wileyonlinelibrary.com]

LINKED CONTENT

This article is linked to Moon et al and Li et al papers. To view these articles, visit <https://doi.org/10.1111/apt.15639> and <https://doi.org/10.1111/apt.15661>.

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